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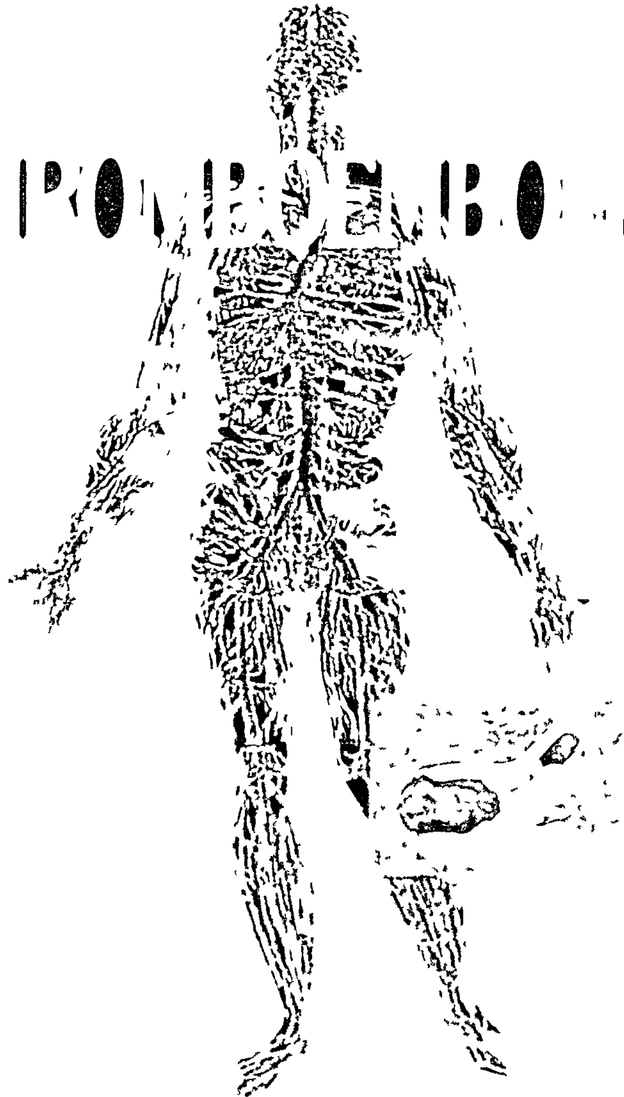
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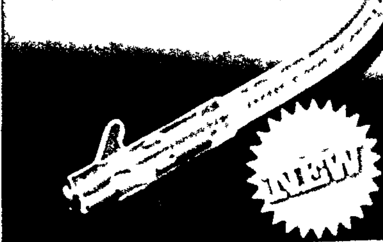
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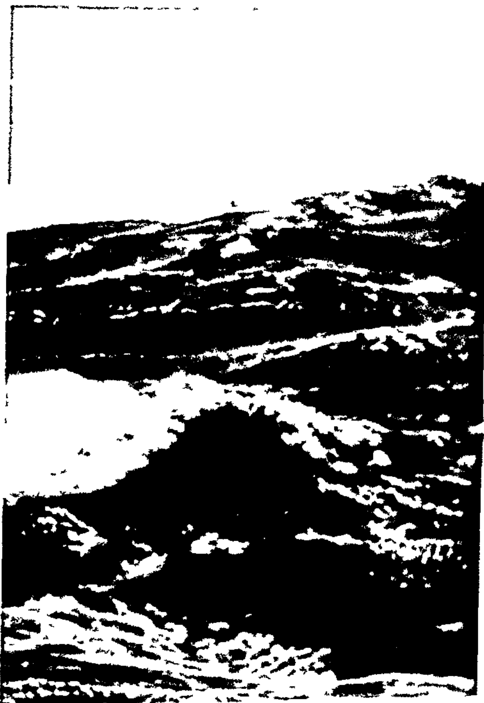
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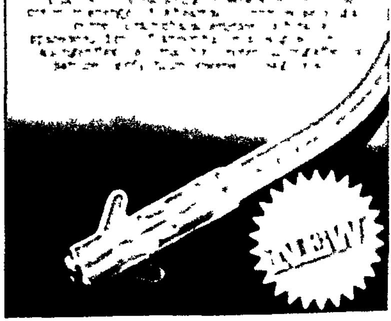
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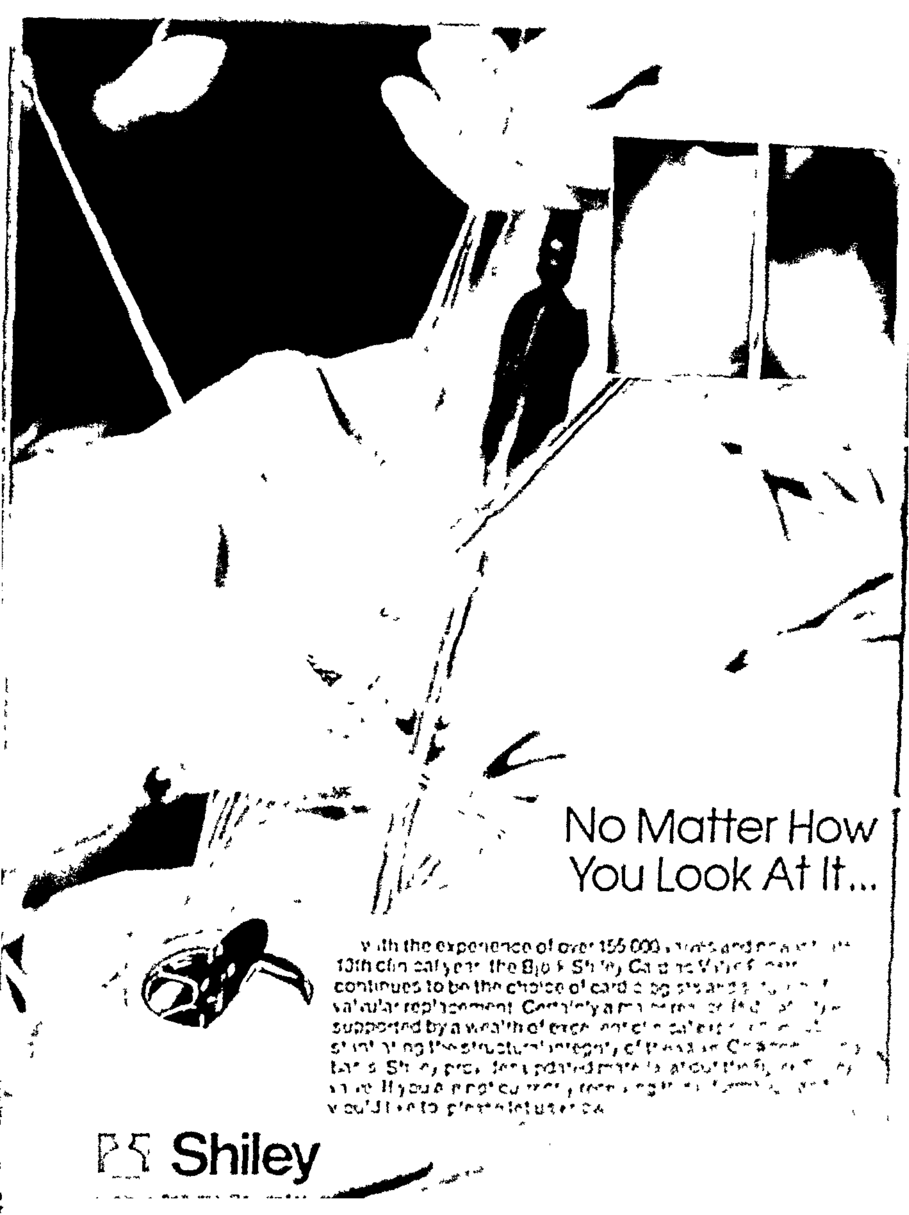




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Editorial

The comeback of hydralazine

Jan Koch Weser M D
Strasbourg France

In most patients with chronic primary hypertension abnormally high peripheral vascular resistance is the proximate cause of elevated arterial pressure[1-3] Their cardiac output is generally within the normal range although it may have been elevated in the early stages of their disease and may become subnormal should cardiac failure supervene The arterial pressure of hypertensive patients can be lowered either by decreasing cardiac output or by lowering total peripheral resistance but the former approach adds a second hemodynamic abnormality to compensate for the existing disturbance The circulation of the chronic hypertensive patient whose arterial pressure has been normalized by depressing cardiac output is doubly abnormal vascular resistance remains excessive and cardiac output is now abnormally low This situation is inescapably associated with decreased tissue perfusion quite probably including heart brain and kidneys hardly a desirable long term hemodynamic goal It would seem preferable to return the excessive total peripheral resistance to normal That is to say drug therapy of established primary hypertension should dilate arterioles

With the exception of propranolol all antihypertensive drugs are vasodilators However most of them act by decreasing the sympathetic stimulation of veins heart and arterioles Thereby they tend to decrease both cardiac output and peripheral resistance The relative hypotensive contribution of these two mechanisms varies greatly It depends on a host of factors including the specific drug and its dose the duration of therapy the patient s hemodynamic characteristics prior to therapy the state of his vasculature and his body position Nevertheless in antihypertensively effective doses any sympathodepressant—regardless of whether it acts by decreasing vasomotor outflow by ganglionic blockade by interfering with norepinephrine release from sympathetic nerve endings or by antagonism at adrenergic receptors—cannot fail to depress cardiac output whenever adrenergic stimulation of capacitance vessels and heart is normally important in maintaining it This is always true in the upright posture and during exercise but in many hypertensive patients it applies even during supine rest

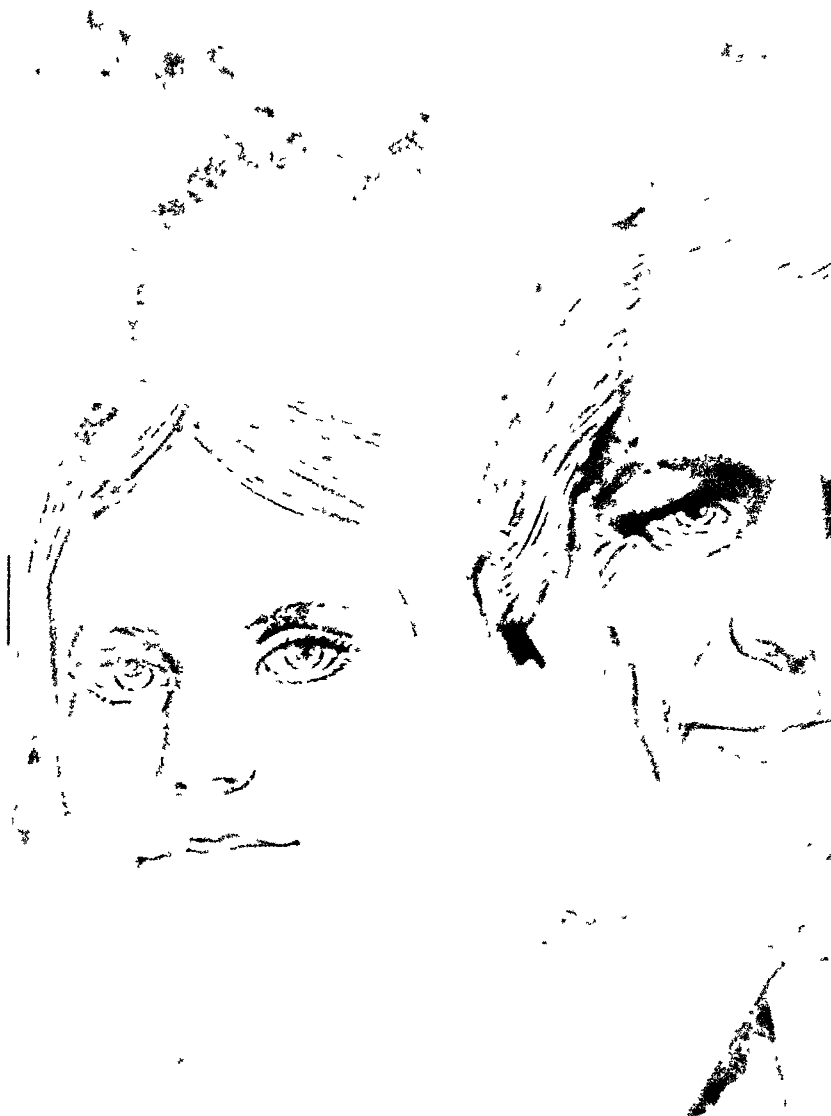
If the desired hemodynamic effect in antihypertensive therapy is dilation of abnormally constricted arterioles why not chose a drug that relaxes arteriolar smooth muscle specifically without affecting the heart or the venous system? Why not pick a compound that acts directly on smooth muscle so that its efficacy will be independent of the vasoconstrictor mechanisms operating? Hydralazine is such a drug and having become available 25 years ago is one of the oldest antihypertensives However it is only now reaching its full potential

A bit of luck marked the introduction of hydralazine into clinical therapy The drug was launched for treatment of hypertension rather than being thrown into the quixotic attack on peripheral arterial insufficiency caused by structural arterial changes that has given vasodilators a bad name It was soon found that hydralazine

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dosages of up to 300 mg should only be administered to fast acetylators

Other untoward effects of hydralazine such as headache dizziness flushing nasal congestion palpitations increases in cardiac work and oxygen consumption anginal attacks and electrocardiographic changes of myocardial ischemia are all related to the vasodilator action of the drug or to the reflex responses to that action They are no problem when low doses of hydralazine are administered to patients treated with propranolol Even hypertensive patients with limited coronary reserve and with symptoms or signs of myocardial ischemia can be successfully treated with this combination of drugs[4 6]

One drawback of hydralazine as antihypertensive therapy has been the practice of administering 4 doses per day This dosage schedule was presumed necessary because of the two to five hour half life of hydralazine in the plasma of most subjects However the drug has special affinity for arterial smooth muscle and persists longer there than in the blood The half time of the antihypertensive action of hydralazine is far longer than the plasma elimination half life Not surprisingly two daily doses of hydralazine are quite sufficient for good blood pressure control during chronic therapy Happily the same has also been shown for propranolol

Treatment of hypertension with direct and specifically acting vasodilator drugs is now receiving the attention it deserves More than a dozen such drugs are under study for this purpose Some of them may ultimately turn out to be more effective and safer than hydralazine For the present hydralazine is one of the most valuable antihypertensive agents and the first one that has come back

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different subjects is meaningless Consequently control readings were given an arbitrary value of 100 and the readings during isometric and dynamic exercise were expressed as a percentage of the control value immediately preceding the exercise Arterial blood pressure was measured by sphygmomanometry before during and after sustained isometric handgrip exercise the cuff being applied to the non exercising arm

For the isometric exercise studies each subject s maximum grip strength (MVC) was ascertained and the dynanometer was set at 30 per cent of this value The standard strain gauge dynamometer is similar to that used in previous studies The original indicating mechanism is replaced by a miniature linear displacement transducer whose electrical output is measured on a voltmeter scale calibrated from 0 to 50 kg A 50 kg thrust produces a 5 mm displacement

After a 30 minute rest period control values for heart rate blood pressure and S_1 amplitude were obtained and the subject was then instructed to maintain 10 per cent MVC for three minutes using his right hand Further readings were taken during the final 30 seconds of handgrip and again four minutes later Care was taken to ensure that the subjects did not perform a Valsalva maneu ver as has been emphasized previously This level of muscular effort has consistently been shown to elicit significant increases in heart rate and blood pressure

After resting for 20 minutes the control obser vations were repeated following which the subjects exercised in the erect posture on a bicycle ergometer at an initial load of 600 kilo pond meters (k p m) while maintaining a pedal speed of 50 to 60 rpm The load was increased by 150 k p m every minute until a heart rate of 170 beats per minute was attained The post exercise recordings of electrocardiogram and phonocar diogram were made one minute after the comple tion of exercise and again 20 minutes later This level of dynamic exercise has been shown to approximate to 70 per cent maximal oxygen consumption

Thirty minutes after the end of exercise a control reading was taken and propranolol (Inderal) was then administered intravenously in a dose of 0 2 mg per kg of body weight over a period of five minutes in a total volume of 30 ml This dose has been shown to produce a potent



Fig 1 The ultra low frequency phonocardiogram *(lower tracing) Above* electrocardiogram

beta adrenergic blocking effect [3] Five minutes after completion of the injection the above sequence of maneuvers and recordings was repeated Although under these circumstances it is clear that a steady state is not achieved the resting values for the amplitude of S_1 before isometric and dynamic exercise following admin istration of the drug were virtually identical suggesting that at rest the effects of the drug were comparable at these times

The results for the individual are expressed as the mean value ± one standard deviation and for the group as a whole as the mean value ± one standard error of the mean The significance levels of the hemodynamic responses to the various interventions and comparisons of these responses before and after propranolol were calculated by Student s paired t test using a Burroughs desk top computer (C 3660) following log transformation of the data

Results

Fig 1 illustrates the configuration of the ultra low frequency phonocardiogram The results are summarized in Tables I to III and Figs 2 and 3

A Effects of dynamic exercise One minute after the cessation of bicycle exercise group mean heart rate was 104 beats per minute compared with a control value of 66 beats per minute ($p < 0.001$) (Table I) On average the S ampli tude increased by 107 ± 27 per cent ($p < 0.001$) (Table I Figs 2 and 3)

After propranolol dynamic exercise increased group mean heart rate from 64 to 79 beats per minute ($p < 0.02$) (Table I) a change which was significantly less than that occurring during exer cise before the administration of the drug (p

Table I Effects of dynamic exercise

Subject	Mode	*Before propranolol*		Mode	*After propranolol*	
		Heart Rate (min)	*S amplitude (%)*		*Heart rate (min)*	*S amplitude (%)*
1	Control	83	100(9)	Control	[illegible]3	100(12)
	Exercise	104	[illegible](31)	Exercise	91	144(16)
	Control	61	100(9)	Control	6[illegible]	100(17)
	Exercise	109	285(11)	Exercise	86	1[illegible]9([illegible]4)
3	Control	62	100(6)	Control	63	100(9)
	Exercise	91	148([illegible]0)	Exercise	84	110([illegible]2)
4	Control	6[illegible]	100(15)	Control	60	100(14)
	Exercise	115	1[illegible]8(11)	Exercise	80	124(9)
5	Control	58	100(1[illegible])	Control	56	100(20)
	Exercise	66	140(9)	Exercise	49	172(12)
6	Control	[illegible]1	100(15)	Control	63	100(10)
	Exercise	139	261(14)	Exercise	83	130(11)
Group	Control	66(4)	100	Control	64(2)	100
	Exercise	104(10)	[illegible]0[illegible](25)	Exercise	[illegible]9(6)	143(11)
	Change	+38(9)	+10[illegible]([illegible])	Change	+15(4)	+43(9)
	p	< 0.001	< 0.001	p	< 0.0[illegible]	< 0.005

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

the average systolic blood pressure increased from 107 to 120 mm Hg during handgrip ($p < 0.05$) (Table II) and average diastolic blood pressure increased from 75 to 93 mm Hg ($p < 0.001$) (Table II). These changes were not significantly different from the changes which occurred during handgrip before the administration of propranolol ($p > 0.10$ for both) (Fig. 2). After propranolol there was no significant change in the amplitude of S during handgrip ($p > 0.98$) (Table II, Fig. 2). This response was also not significantly different from that observed before the drug was given ($p > 0.10$) (Fig. 2).

C. Effects of propranolol at rest. Propranolol produced a significant reduction in mean resting heart rate from 76 to 67 beats per minute ($p < 0.005$) (Table III). There was no significant change in systolic ($p > 0.20$) or diastolic ($p > 0.60$) blood pressure for the group as a whole (Table III). At rest, propranolol reduced the amplitude of S by 20 ± 6 *per cent* ($p < 0.01$) (Table III, Fig. 2).

Discussion

The traditional view that the first heart sound (S) is caused by atrioventricular valve closure has been questioned in recent years, largely because of the observation that the initial vibrations of S do not begin until after these valves are completely closed.[1] Several investigators have suggested that the vibrations which are detected at the precordium as heart sounds are in fact generated by those intracardiac forces which are responsible for accelerating and decelerating the heart and great vessels and the blood contained within them.[2, 3, 22, 23] Indeed, a close temporal relationship has been demonstrated between events in the phonocardiogram and the acceleration and deceleration of blood flow in the central aorta. On the basis of these results and theoretical considerations, it appears that the production of heart sounds is closely related to the phenomenon of acceleration in the central circulation.

In the present study, the ultra low frequency phonocardiogram was recorded in the form of the precordial acceleration tracing, whose configuration has been described by previous workers.[3, 15] This tracing responds to instantaneous changes in the acceleration of the precordium throughout the cardiac cycle and closely resembles the pattern of the second time derivatives of the aortic pressure pulse and of precordial displacement records.[2] The precordial accelerocardiogram possesses some important practical advantages over more familiar techniques for

Table I Effects of dynamic exercise

Subject	Mode	Before propranolol: Heart Rate (min⁻¹)	Before propranolol: S amplitude (%)	Mode	After propranolol: Heart rate (min⁻¹)	After propranolol: S amplitude (%)
1	Control	83	100(9)	Control	73	100(12)
	Exercise	104	2[illegible] (31)	Exercise	91	144(16)
2	Control	61	100(9)	Control	66	100(1[illegible])
	Exercise	109	285(11)	Exercise	86	179(24)
3	Control	62	100(6)	Control	63	100(9)
	Exercise	91	149(20)	Exercise	84	110(22)
4	Control	62	100(15)	Control	60	100(14)
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5	Control	58	100(12)	Control	56	100(20)
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Group	Control	66(4)	100	Control	64(2)	100
	Exercise	104(10)	207(25)	Exercise	79(6)	143(11)
	Change	+38(9)	+10[illegible] (27)	Change	+15(4)	+43(9)
	p	< 0.001	< 0.001	p	< 0.02	< 0.005

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data

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In the present study the ultra low frequency phonocardiogram was recorded in the form of the precordial acceleration tracing whose configuration has been described by previous workers.[1, 15] This tracing responds to instantaneous changes in the acceleration of the precordium throughout the cardiac cycle and closely resembles the pattern of the second time derivatives of the aortic pressure pulse and of precordial displacement records.[2] The precordial accelerocardiogram possesses some important practical advantages over more familiar techniques for

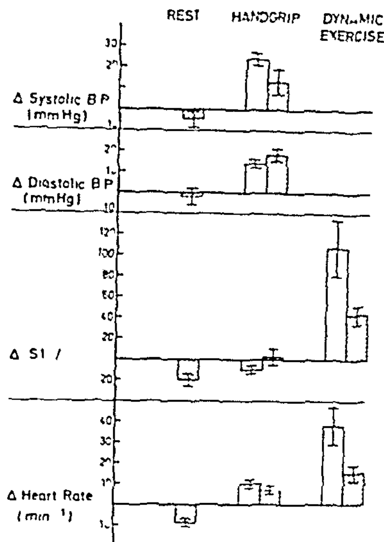


Fig 2 Hemodynamic effects of handgrip dynamic exercise and propranolol *Left hand column* represents effects of propranolol at rest *center column* the effects of handgrip and *right hand column* the effects of dynamic exercise *Blocks* represent the group mean change in blood pressure heart rate and S amplitude and *bars* represent the standard error of the mean *Clear blocks* represent the effects of exercise before propranolol and *shaded blocks* represent the changes after propranolol

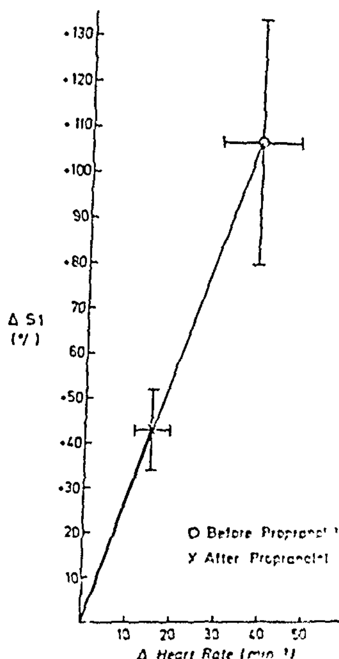


Fig 3 Effect of propranolol on the response to [illegible] exercise *Circle and cross* represent group mean [illegible] *bars* represent standard error of the mean

< 0 005) (Figs 2 and 3) After the drug dynamic exercise increased the amplitude of S by 43 ± 9 per cent (p < 0 005) (Table I) which again was significantly less than the increase observed before the drug was administered (p < 0 02) (Figs 2 and 3)

For the group as a whole there was equivalent suppression of the chronotropic and phonocardiographic responses to dynamic exercise by propranolol (Fig 3)

B Effects of handgrip Handgrip increased group mean heart rate from 69 to 79 beats per minute (p < 0 005) (Table II) Group mean systolic blood pressure increased from 114 to 1[illegible] mm Hg (p [illegible] 0 001) and diastolic blood pressure increased from 77 to 91 mm Hg (p [illegible] 0 001) (Table II) The S *amplitude decreased* on average by 10 ± 4 per cent a change which was just statistically significant (p [illegible] 0 05) (Table II Fig 2) Although the numbers were small there was no correlation between the individual changes in the amplitude of S and the changes in heart rate and blood pressure

After propranolol handgrip increased group mean heart rate from [illegible] to [illegible] beats per minute (p [illegible]) (Table II) which was not significantly different from the response observed before the drug (p [illegible]) (Fig 2) After the drug [illegible]

supine position (Table III Fig 2) which confirms previous observations made in animals ⁵ Interestingly the drug has also been shown to decrease peak aortic acceleration in dogs ³ ⁴ A depressant effect of propranolol on the normal human heart has been demonstrated previously by Parker and associates⁷ in a small group of resting subjects Whether this observation reflects the presence of significant cardiac sympathetic tone at rest or a depressant effect of propranolol independent of its beta adrenergic blocking properties remains conjectural

Isometric handgrip exercise has been employed in many cardiac laboratories as a stress test for the evaluation of left ventricular performance ⁵ ² Previous workers have shown that the normal left ventricular response to isometric exercise includes an increase in contractile state ⁵ ⁴ In most studies this conclusion has been reached by the construction of ventricular function curves ¹ but these are thought to be unreliable in defining left ventricular contractile state in situations in which aortic pressure is changing as it is during isometric handgrip More convincing evidence of an increase in left ventricular contractility during handgrip is the observation that the isovolumetric indices of contractility are increased This increase in contractile state was not reflected in an increase in the amplitude of S (Table II) Our failure to show an increase in S amplitude was certainly not due to an inadequate level of isometric exercise since the magnitudes of the tachycardia and pressor response observed in the present study were similar to those reported previously ⁵ Acute increases in blood pressure induced by the infusion of vasoconstrictor drugs have previously been shown to reduce the intensity of the high frequency components of S which might suggest that the effect of the pressor response on the amplitude of S outweighs and obscures any cardiac inotropic effects of handgrip However sustained increases in peripheral vascular resistance have been shown not to influence either the amplitude of the low frequency components of S or its hemodynamic equivalent peak aortic acceleration ²⁰ Furthermore we have previously shown that those cardiac patients in whom left ventricular function is well maintained respond to handgrip with an increase in S, amplitude despite increases in blood pressure comparable with those occurring in normal subjects ³⁴ This suggests that the rise in blood pressure per se is not responsible for the decline in S amplitude in these young normal subjects Direct measurements of peak aortic acceleration during handgrip may help to clarify the situation

The different effects of beta adrenergic blockade on the cardiac responses to isometric and dynamic exercise observed here lends support to the view that in contrast to dynamic exercise beta adrenergic activation contributes little to the adaptation to the stress of isometric handgrip In fact no significant change could be seen in the response to handgrip after propranolol as regards heart rate blood pressure or S amplitude (Fig 2) Previous studies involving the use of beta adrenergic blocking drugs have shown that the tachycardia associated with sustained isometric handgrip is relatively independent of the beta adrenergic nervous system in normal subjects ²² Beta blockade has also been shown not to impair the pressor response to handgrip but under these circumstances an increase in peripheral vascular resistance makes a greater contribution and an increase in cardiac output a lesser one to the rise in blood pressure ⁵ ³ furthermore plasma catecholamine levels do not increase impressively during sustained handgrip in young normal

Table III Effects of propranolol at rest

Subject	Mode	Heart rate (min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	S amplitude (%)
1	Control	85	118	84	100(12)
	Propranolol	78	98	60	83(12)
2	Control	8[illegible]	130	8[illegible]	100(10)
	Propranolol	69	125	8[illegible]	59(14)
3	Control	[illegible]	90	5[illegible]	100(9)
	Propranolol	66	90	60	7[illegible](12)
4	Control	73	118	70	100(1[illegible])
	Propranolol	64	110	70	95(15)
5	Control	60	10[illegible]	8[illegible]	100(9)
	Propranolol	60	110	[illegible]0	75(10)
6	Control	[illegible]9	110	85	100(8)
	Propranolol	67	110	8[illegible]	93(7)
Group	Control	[illegible]6(4)	11[illegible](6)	77(5)	100
	Propranolol	67([illegible])	10[illegible](5)	[illegible](5)	80(5)
	Change	−9([illegible])	−5(4)	−2(4)	−20(6)
	p	< 0 005	> 0 [illegible]0 NS	> 0 60 NS	< 0 01

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data.

supine position (Table III Fig 2) which confirms previous observations made in animals [2,23] Interestingly the drug has also been shown to decrease peak aortic acceleration in dogs [5,24] A depressant effect of propranolol on the normal human heart has been demonstrated previously by Parker and associates[27] in a small group of resting subjects Whether this observation reflects the presence of significant cardiac sympathetic tone at rest or a depressant effect of propranolol independent of its beta adrenergic blocking properties remains conjectural

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Subject	Mode	Heart rate (min)	Systolic BP (mm Hg)	Diastolic BP (mm Hg)	S amplitude (%)
1	Control	85	118	84	100(1[illegible])
	Propranolol	78	98	60	83(12)
2	Control	85	130	8[illegible]	100(10)
	Propranolol	69	1[illegible]5	85	59(14)
3	Control	74	90	[illegible]5	100(9)
	Propranolol	66	90	60	[illegible](1[illegible])
4	Control	73	118	[illegible]0	100(16)
	Propranolol	64	110	[illegible]0	9[illegible](15)
5	Control	60	105	8[illegible]	100(9)
	Propranolol	60	110	90	[illegible](10)
6	Control	[illegible]9	110	8[illegible]	100(8)
	Propranolol	67	110	8[illegible]	93(7)
Group	Control	[illegible]6(4)	112(6)	[illegible]7(5)	100
	Propranolol	6[illegible] ([illegible])	107(5)	[illegible](5)	80([illegible])
	Change	−9(2)	−[illegible](4)	−[illegible](4)	−[illegible]0(6)
	p	< 0 005	> 0 20 NS	> 0 60 NS	< 0 01

Figures in parentheses represent 1 standard error of the mean value for the group data and 1 standard deviation for the individual data

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The different effects of beta adrenergic blockade on the cardiac responses to isometric and dynamic exercise observed here lends support to the view that in contrast to dynamic exercise beta adrenergic activation contributes little to the adaptation to the stress of isometric handgrip In fact no significant change could be seen in the response to handgrip after propranolol as regards heart rate blood pressure or S_1 amplitude (Fig 2) Previous studies involving the use of beta adrenergic blocking drugs have shown that the tachycardia associated with sustained isometric handgrip is relatively independent of the beta adrenergic nervous system in normal subjects Beta blockade has also been shown not to impair the pressor response to handgrip but under these circumstances an increase in peripheral vascular resistance makes a greater contribution and an increase in cardiac output a lesser one to the rise in blood pressure furthermore plasma catecholamine levels do not increase impressively during sustained handgrip in young normal

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Recent studies by Riekkinen and Rautaharju[10] indicate that this level is to be preferred over the fourth intercostal space when the subject is supine The three orthogonal leads were recorded simultaneously on magnetic tape Recording techniques and equipment were standardized in all institutions to insure uniformity of results Methods of data acquisition and details of computational procedures have been described previously A Control Data Corporation 3200 digital computer was used to obtain 333 different scalar and vectorial measurements for each record comprising practically all parameters previously advocated for analysis of electrocardiograms

Vectorcardiographic notations followed the recommendations of the American Heart Association s Committee on Electrocardiography Reference frames for spherical coordinates and planar vectors are shown in Fig 2 The left sagittal plane was used Measurements in scalar x y z leads included amplitudes and durations of waveforms Q/R and R/S amplitude ratios and the amplitude sum of R + R The reference level for all QRS measurements was the P R segment at the beginning of this complex P and ST T segment measurements were referred to the level of the T P interval

Instantaneous QRS vectors were determined at 0 01 0 02 0 03 and 0 04 second intervals from the onset and in a retrograde fashion from the end of this complex Planar magnitudes of these vectors were computed from the corresponding scalar components Instantaneous ST T vectors were obtained at 0 02 0 04 and 0 06 second intervals from the J point To improve comparability of QRS and ST T vectors in different individuals these complexes were also time normalized by dividing their total durations into eight equal time segments regardless of the absolute values The mean amplitudes of vectors in the end of each time segment were used for graphic representation of the total QRS T complex

Maximal P QRS and T vectors were determined in space and in the three projection planes These vectors represent the vectors of the largest magnitude drawn from the origin of the QRS loop (E point) Half area QRS vectors were also calculated in each projection plane These vectors originate from the E point bisect the total QRS loop area and usually lie in close approximation to the true mean spatial QRS vector

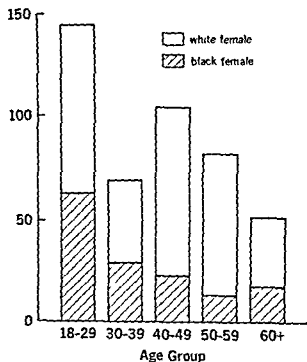


Fig 1 Age and race distributions of 4_0 normal women *The shaded area* in each age group depicts the fraction that was black.

Direction of inscription of the QRS loop in three plane projections was determined using the principle of vector multiplication Means standard deviations and 96 percentile ranges of amplitude items were computed from the total number of measurements available Mean angles and 96 percentile angular ranges were determined by center of gravity method and by examining in detail histograms of distributions Ninety six percentile ranges correspond to a mean ±2 standard deviations whenever a normal distribution is present Since most electrocardiographic data exhibit skewed distributions the use of these ranges instead of standard deviations is a more practical and realistic description of normality

Statistics from women were compared with those of 510 normal men Significance of differences between the samples was determined by Kolmogorov Smirnov s two sample test for amplitudes and by F tests for vector angles

Results

Scalar planar and spatial measurements are presented in Tables I V More emphasis is given to scalar measurements because of their ease of application in daily clinical practice QRS loop rotations are presented in Table VI A compar

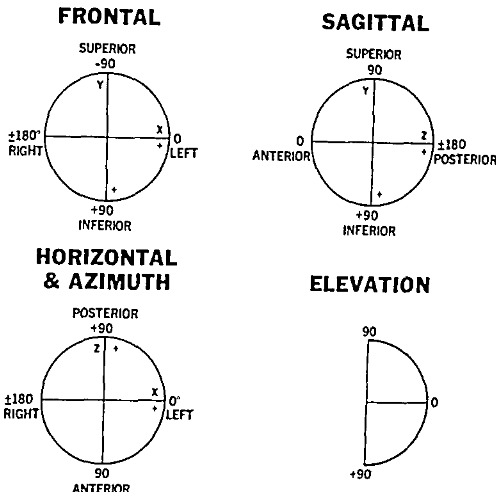


Fig 2 Reference frames for vector directions and orientations

ison is made between these results and those of 510 normal age matched men* and the sex specific limits of clinical importance are summarized in Table VII *

Scalar measurements Table I represents amplitudes and durations of waveforms in x y z leads Also shown are Q/R and R/S amplitude ratios and the amplitude sum of R + R The latter measurement was found to be a useful indicator of left ventricular hypertrophy in a previous study of patients with hypertensive cardiovascular disease Q waves were absent in 47 per cent of the normal records in either Lead x or y They were also absent in 4 cases (1 per cent) in Lead z corresponding to the absence of initial R waves in the right precordial leads S waves occurred more frequently in Lead x (70 per cent) than in Lead y (56 per cent) In addition 9 cases (2 per cent) had also had an S wave in Lead z (corresponding to RR patterns in right precordial leads) with a normal QRS duration

* A list of additional measurements not reported in this communication may be obtained from the authors upon request

Amplitudes of instantaneous QRS and ST T vectors are shown in Table II Time intervals appear in Table III

Planar and spatial measurements Planar amplitudes and directions of maximal P QRS and T as well as half area and instantaneous QRS vectors are shown in Table IV Spherical coordinates of maximal vectors appear in Table V It should be noted that planar amplitudes of instantaneous vectors are determined from scalar components of the corresponding leads rather than vector loops Measurements of these vectors from time markings of the vector loops frequently lead to erroneous results because of difficulties in delineating the closely spaced initial parts of the QRS loop and because of the superimposition of the P and T loop on its early and late portions Furthermore the QRS onset frequently differs from one component lead to another resulting in discrepancies in temporal relationships between corresponding leads and time markings in different plane projections

Initial and terminal QRS vector angles particularly in the frontal plane display wide scatter

Table I Measurements of P QRS and T in orthogonal x y z leads

Item	x lead	y lead	z lead
P amplitude	0.05 ± 0.02‡ 0.02 → 0.09§	0.09 ± 0.04 0.02 → 0.17	*Positive component* 0.03 ± 0.02 0 → 0.08 *Negative component* −0.03 ± 0.02 −0.07 → 0
Q amplitude	−0.08 ± 0.05(237)‖ −0.22 → −0.01	−0.08 ± 0.05(238) −0.23 → −0.01	−0.31 ± 0.17(446) −0.77 → −0.07
R amplitude	0.94 ± 0.35 0.35 → 1.75	0.81 ± 0.33 0.27 → 1.55	0.68 ± 0.25 0.22 → 1.25
S amplitude	−0.17 ± 0.11(319) −0.47 → −0.01	−0.17 ± 0.12(252) −0.52 → −0.01	−0.19 ± 0.17(9) −0.60 → −0.04
T amplitude	0.22 ± 0.10 0.05 → 0.44	0.16 ± 0.09 −0.03 → 0.39	−0.08 ± 0.10 −0.31 → 0.10
Q/R amplitude ratio	0.07 ± 0.04(237) 0.01 → 0.18	0.09 ± 0.06(238) 0.01 → 0.22	0.54 ± 0.42(446) 0.10 → 1.73
R/S amplitude ratio	11.36 ± 18.00(319) 1.12 → 71.70	9.20 ± 13.00(252) 0.64 → 56.00	4.00 ± 3.30(9) 0.70 → 12.00
Q duration†	0.016 ± 0.003(237) 0.010 → 0.024	0.017 ± 0.004(238) 0.009 → 0.028	0.030 ± 0.008(446) 0.014 → 0.047
R duration	0.045 ± 0.012 0.028 → 0.071	0.050 ± 0.014 0.028 → 0.081	0.048 ± 0.010 0.028 → 0.069
S duration	0.029 ± 0.009(319) 0.012 → 0.048	0.028 ± 0.090(252) 0.012 → 0.049	0.028 ± 0.009(9) 0.018 → 0.044
R peak time (intrinsicoid deflection)	0.037 ± 0.005 0.028 → 0.048	0.039 ± 0.005 0.027 → 0.050	0.048 ± 0.006 0.036 → 0.062
R + R	1.60 ± 0.4 0.87 → 2.50		

Amplitudes are in millivolts.
†Durations are in seconds.
‡The mean and standard deviation of each item are shown on the upper line.
§The second line indicates the limits of 96 percentile range.
‖Figures in parentheses show the actual number of observations. Results not followed by a number in parentheses were obtained from total series.

throughout 360 degrees The normal ranges of these angles are therefore too large to be of any practical use Separation of the loops according to different rotation did not significantly decrease the normal angular ranges Significant sex differences in angular directions are discussed in detail in later paragraphs

Direction of inscription of QRS loops in three projection planes is shown in Table VI A variety of rotations occurred in the frontal plane but in the sagittal and horizontal planes practically all the loops were inscribed counterclockwise No clockwise loop was observed in the horizontal plane and the incidence was less than 2 per cent in the sagittal plane Figure-of-eight loops (both clockwise then counterclockwise and counterclockwise then clockwise) were extremely rare in the horizontal plane They occurred infrequently in the sagittal plane and then in the majority of the cases were inscribed counterclockwise in the initial part

Comparison with normal men Comparison with normal men shows that statistically significant differences in most scalar and vectorial items exist between both sexes Many of these differences however are of limited practical use because of the large overlap of normal ranges of men and women In Table VII therefore only distinct sex specific limits which can be easily obtained from scalar and vectorcardiographic plane displays are listed for practical applications

As seen in this table the mean spatial magnitude of maximal QRS is 22 per cent (0.38 millivolt) and mean maximal T is 35 per cent (0.16 millivolt) less in women than in men This difference is reflected in all scalar leads and plane projections Thus the upper normal limits of R

Table II Scalar amplitudes of initial and terminal instantaneous QRS vectors and point J (P R segment as reference level) and instantaneous ST vectors (T P segment as reference level)

	x lead	*y lead*	*z lead*
Initial vectors from the onset of QRS			
0 01 sec	−0 01 ± 0 05	0 ± 0 06	−0 11 ± 0 06
	−0 11 → 0 10	−0 13 → 0 12	−0 23 → 0 01
0 02 sec	0 16 ± 0 16	0 10 ± 0 14	−0 22 ± 0 16
	−0 13 → 0 56	−0 13 → 0 45	−0 51 → 0 14
0 03 sec	0 62 ± 0 27	0 44 ± 0 26	−0 13 ± 0 31
	0 10 → 1 25	−0 01 → 1 07	−0 66 → 0 65
0 04 sec	0 77 ± 0 41	0 63 ± 0 38	0 39 ± 0 36
	0 → 1 70	−0 08 → 1 46	−0 53 → 1 10
Terminal vectors from the end of QRS			
point J	0 00 ± 0 03	0 00 ± 0 03	0 01 ± 0 03
	−0 06 → 0 05	−0 06 → 0 06	−0 07 → 0 04
0 01 sec	−0 01 ± 0 05	0 ± 0 08	0 09 ± 0 07
	−0 12 → 0 11	−0 15 → 0 14	−0 07 → 0 22
0 02 sec	−0 03 ± 0 15	0 ± 0 17	0 31 ± 0 17
	−0 27 → 0 36	−0 28 → 0 38	−0 04 → 0 62
0 03 sec	0 19 ± 0 38	0 21 ± 0 32	0 52 ± 0 26
	−0 29 → 1 18	−0 35 → 0 97	−0 05 → 1 04
0 04 sec	0 61 ± 0 48	0 53 ± 0 40	0 44 ± 0 36
	−0 25 → 1 61	−0 29 → 1 32	−0 31 → 1 16
Instantaneous ST vectors			
0 02 sec after	−0 02 ± 0 07	−0 03 ± 0 04	−0 01 ± 0 05
point J	−0 10 → 0 06	−0 12 → 0 07	−0 09 → 0 07
0 04 sec after	−0 01 ± 0 07	−0 03 ± 0 05	−0 02 ± 0 04
point J	−0 09 → 0 07	−0 12 → 0 07	−0 09 → 0 05
0 06 sec after	0 ± 0 08	−0 02 ± 0 07	−0 02 ± 0 04
point J	−0 08 → 0 07	−0 11 → 0 07	−0 10 → 0 05

R_y and R amplitudes are 11 per cent (0 22 millivolt) 20 per cent (0 40 millivolt) and 30 per cent (0 54 millivolt) less respectively in women than in men The lower normal limit of R is 30 per cent (0 16 millivolt) and mean T amplitude is 70 per cent (0 20 millivolt) smaller in women The upper normal limit of maximal QRS in this group is less than that of men by 14 per cent (0 34 millivolt) in the frontal 24 per cent (0 71 millivolt) in the sagittal and 17 per cent (0 36 millivolt) in the horizontal plane

Figs 3 and 4 show reconstructed mean QRS T deflections and vector loops comparing normal men and women The smaller scalar deflections and vector loops in women are readily seen in these illustrations It is also seen that mean vectors at the end of QRS (point J) are more posterior and superior in women

Despite small mean differences the general direction of the maximal and half area QRS vectors is strikingly similar in both sexes Mean

Table III Time intervals obtained from three simultaneously recorded leads Onset and end of each electrocardiographic waveform were taken at the earliest and latest departure from the baseline in any one of the three leads

Item	*Measurement (sec)*
P duration	0 10[illegible] ± 0 019
	0 064 → 0 14[illegible]
P R interval	0 154 ± 0 0[illegible]
	0 112 → 0 208
P R segment	0 048 ± 0 018
	0 020 → 0 0[illegible]
QRS duration	0 084 ± 0 008
	0 068 → 0 101
Q T interval (uncorrected)	0 3[illegible]2 ± 0 02[illegible]
	0 319 → 0 4[illegible]

ST vectors are more superiorly and posteriorly directed in women than in men (Fig 3) In contrast to men who normally have negative T waves in Lead z, women may have a flat or slightly positive T in this lead as a normal variant The normal ranges of the maximal T vector angle in the horizontal and sagittal planes are larger in this group and extend from anterior to posterior and from inferior to superior (Table VII)

In women Q waves in Leads x and y and S waves in Lead x occur less frequently and the upper normal limit of QRS duration is 8 milliseconds shorter than in men Mean Q wave duration in Leads x and y is also significantly shorter in this group but large variances in this parameter invalidate its use as a differential diagnostic tool

Discussion

Differences in electrocardiograms of men and women are frequently ignored in routine interpretations This is mainly due to the lack of well defined sex specific normal limits

While such limits for normal men have been well established in both conventional and orthogonal leads a comprehensive study of the latter lead system in women is non-existent In the largest series of normal men and women published by von der Groeben and associates only means and standard deviations are reported which do not lend themselves to an estimate of realistic normal ranges This is due to the fact that most of the electrocardiographic data are not

Table IV Planar amplitudes and directions of the maximal vectors and half area and instantaneous QRS vectors. Planar amplitudes of instantaneous QRS vectors are determined from scalar components (see text)

Item	Frontal		Left Sagittal		Horizontal	
	Amplitudes	Angles	Amplitudes	Angles	Amplitudes	Angles
Maximal P Vector	0.01 ± 0.04	61†	0.10 ± 0.04	96	0.06 ± 0.02	14
	0.04 → 0.19	0 → 93†	0.03 → 0.18	1[illegible]8 → 44	0.03 → 0.12	115 → −98
Maximal QRS Vector	1.24 ± 0.38	41	1.00 ± 0.31	125	1.10 ± 0.32	29
	0.63 → 2.19	10 → 88	0.49 → 1.70	−156 → 48	0.55 → 1.84	114 → −35
Maximal T Vector	0.28 ± 0.11	32	0.20 ± 0.08	62	0.25 ± 0.10	−17
	0.10 → 0.57	2 → 68	0.07 → 0.42	170 → −88	0.09 → 0.49	4[illegible] → −70
Half Area QRS Vector	1.12 ± 0.45	4[illegible]	0.93 ± 0.36	120	0.97 ± 0.33	29
	0.22 → 2.20	−1 → 8[illegible]	0.24 → 1.71	−174 → 5[illegible]	0.36 → 1.70	78 → −22
Initial QRS Vectors						
0.01 second	0.07 ± 0.04	−13 ‡	0.13 ± 0.05	−4	0.13 ± 0.05	−95
	0.01 → 0.18	20 → −10	0.03 → 0.24	80 → −58	0.03 → 0.24	−5 → −146
0.02 second	0.23 ± 0.17	28	0.29 ± 0.14	[illegible]4	0.32 ± 0.14	−54
	0.02 → 0.69	−129 → 1[illegible]4	0.04 → 0.62	144 → −30	0.06 → 0.69	38 → −115
0.03 second	0.78 ± 0.3[illegible]	34	0.53 ± 0.27	88	0.6[illegible] ± 0.27	−[illegible]
	0.1[illegible] → 1.51	1 → 64	0.04 → 1.16	156 → 10	0.1[illegible] → 1.32	54 → −57
0.04 second	1.06 ± 0.45	39	0.84 ± 0.35	1[illegible]4	0.96 ± 0.36	30
	0.10 → [illegible].00	−4 → 84	0.10 → 1.59	−168 → 4[illegible]	0.[illegible]0 → 1.[illegible]5	88 → −26
Terminal QRS Vectors						
0.01 second	0.08 ± 0.0[illegible]	−150‡	0.12 ± 0.06	−1[illegible]2	0.11 ± 0.0[illegible]	96‡
	0.01 → 0.[illegible]0	16 → −18	0.01 → 0.24	−3[illegible] → 82	0.01 → 0.23	−98 → −36
0.02 second	0.18 ± 0.14	−169‡	0.36 ± 0.16	−17[illegible]	0.35 ± 0.17	99
	0.03 → 0.55	1[illegible] → −30	0.05 → 0.69	−8[illegible] → 108	0.03 → 0.7[illegible]	−150 → 16
0.03 second	0.45 ± 0.35	63‡	0.64 ± 0.27	163	0.66 ± 0.29	[illegible]
	0.04 → 1.44	−[illegible]0 → −80	0.1[illegible] → 1.24	−1[illegible]4 → 84	0.13 → 1.34	150 → −5
0.04 second	0.90 ± 0.49	43	0.81 ± 0.34	13[illegible]	0.89 ± 0.36	41
	0.06 → 2.00	−[illegible]5 → −160	0.19 → 1.56	−140 → 54	0.18 → 1.75	1[illegible]2 → −[illegible]6

Amplitudes are in millivolts.
†Angles are in degrees. All angular ranges should be read in clockwise sequence.
‡Angles marked by ‡ show no significant clustering as evidenced by wide 96 percentile ranges.

normally distributed. Ranges should preferably be expressed in terms of percentiles. In another report on sex differences in the vectorcardiogram the sample size is not large enough for determination of valid sex specific normal limits. As pointed out previously adequate sample size as well as detailed statistical analysis represents prerequisites for arriving at reliable normal standards.[*] The present study based on the records from 510 men and 450 women should be sufficient for precise demarcation of normal limits in both sexes. Table VII summarized the most important sex differences in the electro-vector cardiographic parameters and can be used as a guideline for differentiation of normal from abnormal. Apart from spatial magnitudes all other variables presented in this table can be manually measured from any record and a comparison can be easily made with the tabulated norms.

Table V Spatial magnitude and orientation of maximal P QRS and T vectors

Item	*Magnitude (millivolts)*	*Azimuth (degrees)*	*Elevation (degrees)*
Maximal P Vector	0.11 ± 0.04	14	49
	0.05 → 0.20	115 → −98	−2[illegible] → 80
Maximal QRS Vector	1.35 ± 0.36	29	34
	0.[illegible]5 → 2.25	114 → −35	−5 → 61
Maximal T Vector	0.33 ± 0.13	−17	31
	0.12 → 0.64	4[illegible] → −70	−15 → 64

Angular ranges should be read in a clockwise sequence.

The larger amplitudes seen in men in practically all scalar and vectorial items indicate that diagnostic criteria of ventricular hypertrophies are of different sensitivity and specificity in men and women. For example the upper limit of normal of the sum of R and R amplitudes was found to be 2.5 millivolts and 3.1 millivolts for

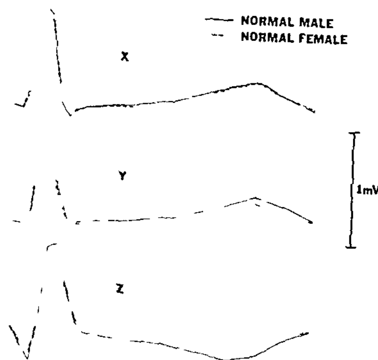


Fig 3 QRS T complexes in normal men and women Figures are constructed from mean amplitude values of each eighth of the QRS and ST T complexes (obtained by dividing the total duration of these complexes into eight equal parts) Data are based on records from 510 normal men and 450 normal women

Table VI Direction of inscription of QRS loops in the frontal left sagittal and horizontal planes in 450 normal women

	Frontal	*Left sagittal*	*Horizontal*
CW	230 (51%)	8 (2%)	0 (0%)
CW/CCW	37 (8%)	12 (3%)	0 (0%)
CCW/CW	61 (14%)	27 (6%)	8 (2%)
CCW	122 (27%)	403 (89%)	442 (98%)

Abbreviation CW = clockwise CW CCW = figure-of-eight clockwise then counterclockwise CCW CW = figure-of eight counterclockwise then clockwise CCW = counterclockwise

women and men respectively a difference of 24 per cent This criterion which was found very useful in the diagnosis of left ventricular hypertrophy [1] obviously needs to be applied differently according to the sex of the patient under study Use of this high voltage criterion with an upper limit derived from males in a female population would decrease its sensitivity drastically

Similar discrepancies in almost all other diagnostic parameters of left ventricular hypertrophy exist between both sexes Low voltage criteria for diagnosis of right ventricular hypertrophy and chronic obstructive pulmonary disease are also affected significantly by these voltage differences

Table VII Sex specific limits Data are derived from records of 510 normal men and 450 normal women unless indicated otherwise in parentheses (P < 001 for all measurements)

Items	*Men*	*Women*
Scalar measurements		
QRS duration	0093 ± 0009	0084 ± 0008
	0076 → 0112	0069 → 0101
Q amplitude†	−041 ± 021	−031 ± 017 (41[illegible])
	−093 → −009	−0[illegible] → −00[illegible]
R amplitude	117 ± 037	091 ± 03[illegible]
	051 → 197	035 → 17[illegible]
R amplitude	103 ± 041	081 ± 033
	03[illegible] → 19[illegible]	027 → 15[illegible]
R amplitude	093 ± 03[illegible]	068 ± 0[illegible]
	036 → 179	022 → 12[illegible]
S amplitude	−027 ± 015 (407)	−017 ± 011 (319)
	−068 → −006	−047 → −001
T amplitude	−028 ± 013	−005 ± 010
	−0[illegible]8 → −00[illegible]	−031 → 010
Q/R amplitude ratio	0[illegible]0 ± 03[illegible]	054 ± 042 (41[illegible])
	010 → 120	010 → 1[illegible]3
R + R amplitude	200 ± 052	160 ± 04[illegible]
	106 → 310	087 → [illegible]
point J in Lead z	−007 ± 004	−001 ± 003
	−017 → 000	−007 → 004
Planar measurements		
Max QRS, amplitude	157 ± 042	121 ± 039
	081 → 2[illegible]3	063 → 219
Max QRS amplitude	132 ± 04[illegible]	100 ± 031
	060 → 242	049 → 171
Max QRS amplitude	139 ± 03[illegible]	110 ± 031
	074 → 219	05[illegible] → 183
Max T amplitude	036 ± 013	020 ± 008
	013 → 06[illegible]	007 → 04
Max T amplitude	040 ± 014	02[illegible] ± 010
	015 → 072	009 → 049
Max T angle‡	38	6[illegible]
	8[illegible] → 0	1[illegible]0 → −88
Max T angle	−46	−17
	−8 → −8[illegible]	4[illegible] → −[illegible]0
Spatial measurements		
Max QRS magnitude	173 ± 044	13[illegible] ± 03[illegible]
	09[illegible] → 27[illegible]	07[illegible] → 22[illegible]
Max T magnitude	04[illegible] ± 016	030 ± 012
	018 → 08[illegible]	009 → 0[illegible]7

Durations are in seconds
†Amplitudes are in millivolts
‡Angles are in degrees

The lower limit of normal for R had been found the most useful criterion both for right ventricular hypertrophy and chronic obstructive pulmonary disease [11] In men this limit was 051 millivolt and in women 035 millivolt If the limit of normal for men was to be applied to a normal female population it is obvious that a substantial number of the latter would be erroneously clas

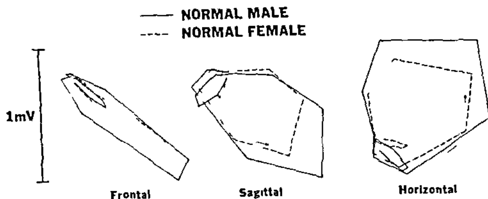


Fig 4 QRS-T loops in three plane projections Figures are constructed from mean planar amplitudes of ¼ divisions of QRS and ST T complexes Data are derived from 510 normal men and 450 normal women

sified as abnormal with a tentative diagnosis of right ventricular hypertrophy or chronic obstructive pulmonary disease These examples indicate that to improve diagnostic performance of the electrocardiogram sex specific limits for high and low voltage are necessary

The smaller amplitudes in women have been ascribed to differences in torso size higher content of body fat and smaller average heart size The mean left ventricular mass was found to be significantly smaller in women than in men [2] The average heart weight was 312 Gm in normal males and 225 Gm in normal females The smaller heart size may also explain the significantly shorter QRS duration seen in women This difference in duration signifies the importance of sex specific limits in the diagnosis of ventricular conduction delays

Scalar analysis shows that in approximately one half of the normal women and one third of the normal men no Q wave in the x and y leads can be found A similar observation in conventional electrocardiograms has been reported by Simonson The absence of the Q wave in these leads is so common in all age and sex groups that no diagnostic significance should be given to this observation Comparative analysis of the Q wave in Lead z shows that initial anterior QRS forces are of lower magnitude in normal women and in 1 per cent of the cases may even be absent in this lead This confirms the finding in the conventional electrocardiogram of a higher incidence of absent initial R waves in some of the right precordial lead in women Such a finding is extremely rare in men The normal electrocardiogram of women therefore should not be confused with anteroseptal myocardial infarctions which reveal similar electrocardiographic features The occurrence of an S wave in Lead z in the presence of normal QRS duration should be considered a normal variant This pattern is more commonly seen in younger adults A delay in activation of the right ventricle has been postulated as its cause

The more superiorly and posteriorly directed point J and ST segment in women may play a role in diagnostic interpretations of exercise electrocardiograms and ischemic patterns Differences found between men and women in the electrocardiographic response to exercise [2] are probably due to these inherent sex differences in the ST segment of the resting electrocardiogram Although the resting electrocardiogram usually serves as control for the exercise response in each individual case the specificity and sensitivity of the test may be enhanced if the criteria of interpretations were modified

Our observation in women of a less anteriorly directed mean maximal T vector in the horizontal plane is comparable to findings by Simonson of a negative mean T wave amplitude in Lead V_1

Some abnormal rotation of the QRS loops was observed in a few of the elderly subjects In this group a certain degree of myocardial fibrosis clinically silent scars and/or fascicular blocks cannot be entirely ruled out It is pertinent to note that a relatively high incidence of left anterior hemiblock in the elderly without manifest cardiovascular diseases has been reported in the literature [3] For the diagnosis of fascicular blocks it is important to realize that normal ranges of maximal QRS vectors differ considerably from ranges derived from conventional 12 lead electrocardiograms Whereas for standard leads a range

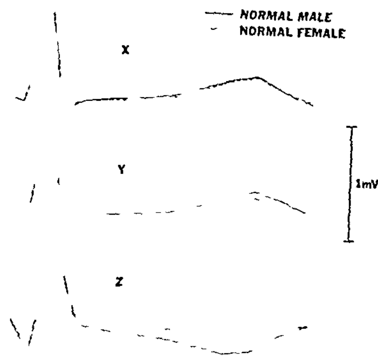


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Similar discrepancies in almost all other diagnostic parameters of left ventricular hypertrophy exist between both sexes Low voltage criteria for diagnosis of right ventricular hypertrophy and chronic obstructive pulmonary disease are also affected significantly by these voltage differences

Table VII Sex specific limits Data are derived from records of 510 normal men and 450 normal women unless indicated otherwise in parentheses (P < 001 for all measurements)

Items	*Men*	*Women*
Scalar measurements		
QRS duration	0 093 ± 0 009	0 084 ± 0 008
	0 076 → 0 112	0 065 → 0 104
Q amplitude†	−0 41 ± 0 21	−0 31 ± 01 (41)
	−0 93 → −0 09	−0 [illegible] → −0 0[illegible]
R amplitude	1 17 ± 0 37	0 94 ± 0 35
	0 51 → 1 97	0 35 → 1 75
R amplitude	1 03 ± 0 41	0 81 ± 0 31
	0 35 → 1 95	0 27 → 1 55
R amplitude	0 93 ± 0 35	0 69 ± 0 [illegible]
	0 36 → 1 79	0.22 → 1 [illegible]
S amplitude	−0 27 ± 0 15 (407)	−0 17 ± 0 11 (319)
	−0 68 → −0 06	−0 47 → −0 01
T amplitude	−0 29 ± 0 13	−0 09 ± 0 10
	−0 58 → −0 06	−0 31 → 0 10
Q/R amplitude ratio	0 50 ± 0 3[illegible]	0 54 ± 0 42 (40[illegible])
	0 10 → 1 20	0 10 → 1 73
R + R amplitude	2 00 ± 0 52	1 60 ± 0 47
	1 06 → 3 10	0 87 → 2 [illegible]
point J in Lead z	−0 07 ± 0 04	−0 01 ± 0 03
	−0 17 → 0 00	−0 07 → 0 04
Planar measurements		
Max QRS amplitude	1.57 ± 0 42	1 21 ± 0 34
	0 81 → 2 53	0 63 → 2 19
Max QRS amplitude	1 32 ± 0 45	1 00 ± 0 31
	0 60 → 2 4[illegible]	0 49 → 1 71
Max QRS amplitude	1.39 ± 0 36	1 10 ± 0 31
	0 74 → 2 19	0 [illegible] → 1 83
Max T amplitude	0 36 ± 0 13	0 20 ± 0 08
	0 13 → 0 6[illegible]	0 07 → 0 4[illegible]
Max T amplitude	0 40 ± 0 14	0 25 ± 0 10
	0 15 → 0 72	0 09 → 0 49
Max T angle‡	38	[illegible]
	87 → 0	170 → [illegible]
Max T angle	−46	−17
	−8[illegible] → −83	4[illegible] → −7[illegible]
Spatial measurements		
Max QRS magnitude	1 73 ± 0 44	[illegible]
	0 9[illegible] → 2 7[illegible]	[illegible]
Max T magnitude	0 46 ± 0 16	0 30 ± 0 1[illegible]
	0 18 → 0 8[illegible]	0 09 → 0 [illegible]

Durations are in seconds
†Amplitudes are in millivolts
‡Angles are in degrees

The lower limit of normal for R had been found the most useful criterion both for right ventricular hypertrophy and chronic obstructive pulmonary disease [illegible] In men this limit was 0 [illegible] millivolt and in women 0 35 millivolt If the limit of normal for men was to be applied to a normal female population it is obvious that a substantial number of the latter would be erroneously cl[illegible]

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from −30 to +110 degrees is considered normal for QRS direction in the frontal plane, the normal range for orthogonal leads extends only from 10 to 75 degrees in males and from 10 to 88 degrees in females. For the diagnosis of left anterior and posterior hemiblock, appropriate normal limits need to be used to detect abnormal left and right axis deviations.

The normal limits of the orthogonal electrocardiogram in women presented here clearly demonstrate the importance of sex specific electrocardiographic criteria for diagnosis of ventricular hypertrophies and conduction delays. The fact that the Q wave in Lead z may be absent in some of the normal women should be considered in evaluation of electrocardiograms for anteroseptal myocardial infarctions. Furthermore, in the detection of coronary artery disease, the electrocardiographic response to exercise may achieve a higher degree of sensitivity and specificity if interpreted in the context of the appropriate limits of normal for men and women.

Summary

Normal limits of the orthogonal electrocardiogram and vectorcardiogram in adult women, ranging in age from 18 to 90 years, are presented. A comparison of results is made with those of normal age matched men, and sex differences are analyzed from a total of 960 normal records (510 men and 450 women). For the majority of scalar and vectorial items, significant sex differences were found which in women included shorter QRS duration, smaller vector loops, and decreased P, Q, R, S, and T deflections. The upper normal limits of R, R, and R amplitudes were 11 per cent, 20 per cent, and 30 per cent less, respectively, in women than in men.

The sensitivity and specificity of electrocardiographic criteria for high and low voltage were significantly affected by these sex differences in amplitudes. For example, as a discriminator between normals and subjects with left ventricular hypertrophy, the upper normal limit of R + R, amplitude sum was 3.10 millivolts in men but 2.50 millivolts in women. Hence the use of the limit derived from males in a female population would decrease its sensitivity drastically. Similar discrepancies existed in the sensitivity and specificity of electrocardiographic criteria for low voltage. Since the lower normal limit of R, amplitude was 0.51 millivolt in men but only 0.35 millivolt in women, a substantial number of normal women would be misclassified as having right ventricular hypertrophy or chronic obstructive pulmonary disease if the limit derived from males was used as a criterion.

The absence of Q waves in Leads x and y was a common finding in each age and sex group and carries no diagnostic significance. While initial anterior QRS forces in Lead z were present in all normal men, they were smaller and even absent in 1 per cent of normal women. Hence greater difficulties in electrocardiographic diagnosis of anteroseptal myocardial infarction in women may be encountered.

Mean vectors at the end of QRS (point J) and early part of the ST segment were more inferiorly and anteriorly directed in men than in women. T waves in Lead z were always negative in men but flat or positive T waves were observed in some of the normal women. Sex differences in the level of point J and the ST segment may have important bearings on the interpretation of exercise electrocardiograms.

The shorter QRS duration in women signified the importance of sex specific limits for ventricular conduction delays.

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Table I Clinical and electrophysiologic data

Pt. no	Age	Diagnosis	Resting ECG	Sinus CL (msec)	A H (msec)	H V (msec)	Antegrade conduction	Retrograde conduction
Group I								
1	55	PSVT	Normal	1250	100	55	WP at ACL 665 msec	1 1 VA up to VCL 375 msec
2	30	PSVT	Normal	680	65	50	315	335
3	60	PSVT	RBBB	880	85	50	400	375
4	34	PSVT	Normal	800	75	45	315	″ 360
5	50	PSVT	RBBB	"00	100	5ɔ	″ 325	″ 3"5
6	47	PSVT	Normal	900	115	50	430	350
7	65	ASHD PSVT	AMI	11?0	115	50	430	WP at VCL 400
8	61	ASHD PSVT	Normal	900	100	50	300	1 1 VA up to VCL 350
9	5?	I SVT	Normal	80	1 0	50	400	370 ″
10	0	ASHD PSVT	Normal	1000	125	40	600	3"0
11	46	PSVT	Normal	900	9ɔ	4ɔ	″ 400	WP at VCL 460
1?	68	ASHD PSVT	LBBB	"00	10	65	545	3 0
13	57	PSVT	Normal	800	8ɔ	5ɔ	380	3ɔ0
Group II								
14	ɔ0	PSVT	Normal	7ɔ0	110	50	4?5	1 1 VA at VCL 3ɔ0
15	54	ASHD I SVT	IMI	80	80	40	460	300
16	17	PSVT	Normal	600	100	4ɔ	400	335
1	14	PSVT	Normal	680	80	45	1 1 AV up to ACL 350	350
Group III								
18	4?	PSVT	Normal	840	85	40	WP at ACL 400	WP at VCL 600
19	29	PSVT	Normal	"00	75	40	330	1 1 VA up to VCL 3/5
20	48	ASHD	ST & T Abnor malities	6?0	0	50	315	3"0

ASHD = art rioscl rotic h rt dise se PSVT = paro ysm l ree trant supra entricula ta hycardia AMI = anterior myoc rdial infa ctio RBBB = right bundl br h block LBBB = left bundl branch block ACL = atrial cycl l gth WP = W nck b ch ph nom non A V = atrioventricular conduct n V A = tric l trial co d tion Pt no = p t ent umber

graphic paper at a speed of 150 mm /sec Using a programmed digital stimulator incremental atrial and ventricular pacing was performed up to the onset of Ant and Ret Wenckebach phenom enon or up to maximum heart rates of 200 beats/min For refractory period determinations com parable basic atrial and ventricular cycle lengths (A A or V V) were scanned with programmed extra timuli (A or V) at decreasing coupling intervals (V A or V V) up to the point of atrial or ventricular muscle refractoriness Care was taken to ground all equipment All procedures were completed without any complications

Definition of terms

The definitions for Ant and Ret conduction times and refractory periods have been pub lished For the present study the following additional measurements were made The inter val between the Ant His (H) bundle potential and the subsequent atrial echo response (H Ae interval) during PSVT was measured both from the onset and the end of H to the onset of low right atrial deflection on the His bundle electro gram (HBE) recording Similarly the following Ae H interval was measured from the onset of respective deflections The onset of the low right atrial electrogram during the Ae or PSVT was relatively easy to identify when the Ae coincided preceded or clearly followed the ventricular elec trogram as occurred in 16 out of 20 patients In the remaining four patients the onset of Ae on the HBE was obscured by the ventricular electro gram and the H Ae interval had to be measured indirectly In these cases the H Ae interval was measured from the H to the onset of the high

Antegrade and retrograde conduction characteristics in three patterns of paroxysmal atrioventricular junctional reentrant tachycardia

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In recent years the electrophysiology of paroxysmal atrioventricular junctional reentrant supraventricular tachycardia (PSVT) has been frequently studied[1-8] The term PSVT has been used in a broad sense and only recently has it been realized that the site of reentry may not necessarily be the atrioventricular (A V) node[9-11] With few exceptions most studies of PSVT have dealt with the analysis of antegrade (Ant) conduction Only rarely *have either the capacity* or the patterns of ventriculo atrial (V A) conduction been documented in these patients The present study deals with both Ant and retrograde (Ret) conduction characteristics in 20 patients with documented PSVT in the absence of ventricular pre excitation The purposes of this report are as follows (1) to describe three distinct patterns of PSVT based upon the relationship between Ant His (H) bundle activation and atrial echo response (Ae) during PSVT (2) to offer a rather simple and reproducible method i e Ant and Ret conduction ratios (Ae H H Ae) for determining the site of reentry during PSVT and (3) to provide comparisons and correlations of Ant and Ret conduction and refractory period patterns in patients with PSVT In addition some interesting and controversial aspects of PSVT *will be discussed*

Materials and Methods

Right heart catheterization was performed in the nonsedated postabsorptive state The nature of the study was explained to all patients and signed consent obtained Electrode catheters were fluoroscopically positioned in the region of the high right atrium tricuspid valve and right ventricular apex for recording local electrical activity and electrical stimulation[12,13] When feasible an additional electrode catheter was positioned in the region of the mid coronary sinus All intracardiac electrograms (filtered at frequency settings of 40 to 500 Hz) standard ECG Leads I II and V_1 and time lines generated at 10 100 and 1000 msec were displayed on a multichannel oscilloscope and recorded on magnetic tape The records were subsequently reproduced on photo

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Table I Clinical and electrophysiologic data

Pt. no	Age	Diagnosis	Resting ECG	Sinus CL (msec)	A H (msec)	H V (msec)	Antegrade conduction	Retrograde conduction
Group I								
1	55	PSVT	Normal	1250	100	55	WP at ACL 665 msec	1:1 VA up to VCL 375 msec
2	30	PSVT	Normal	680	65	50	315	335
3	60	PSVT	RBBB	880	85	50	400	375
4	34	PSVT	Normal	800	75	45	315	360
5	50	PSVT	RBBB	700	100	55	″ 375	″ 375
6	4[illegible]	PSVT	Normal	900	115	50	430	350
7	[illegible]	ASHD PSVT	AMI	1120	115	50	430 ″	WP at VCL 400
8	61	ASHD PSVT	Normal	900	100	50	300	1:1 VA up to VCL 350
9	52	PSVT	Normal	[illegible]80	120	50	400	370
10	[illegible]0	ASHD PSVT	Normal	1000	125	40	600	″ 370 ″
11	46	PSVT	Normal	900	95	45	400	WP at VCL 460
12	68	ASHD PSVT	LBBB	700	105	65	545	370
13	67	PSVT	Normal	800	85	55	380	350
Group II								
14	50	PSVT	Normal	750	110	50	425	1:1 VA at VCL 350
15	54	ASHD PSVT	IMI	[illegible]80	80	40	460	300
16	[illegible]	PSVT	Normal	600	100	45	400	335
17	14	PSVT	Normal	680	80	45	1:1 AV up to ACL 350	350
Group III								
18	42	PSVT	Normal	840	85	40	WP at ACL 400	WP at VCL 600
19	29	PSVT	Normal	700	75	40	330	1:1 VA up to VCL 375
20	48	ASHD	ST & T Abnormalities	620	[illegible]0	50	315	370

ASHD = arteriosclerotic heart disease; PSVT = paroxysmal reentrant supraventricular tachycardia; AMI = anterior myocardial infarction; RBBB = right bundle branch block; LBBB = left bundle branch block; ACL = atrial cycle length; WP = Wenckebach phenomenon; AV = atrioventricular conduction; VA = ventriculoatrial conduction; Pt. no. = patient number.

graphic paper at a speed of 150 mm/sec. Using a programmed digital stimulator, incremental atrial and ventricular pacing was performed up to the onset of Ant. and Ret. Wenckebach phenomenon or up to maximum heart rates of 200 beats/min. For refractory period determinations, comparable basic atrial and ventricular cycle lengths (A A or V V) were scanned with programmed extrastimuli (A or V) at decreasing coupling intervals (A A or V V) up to the point of atrial or ventricular muscle refractoriness. Care was taken to ground all equipment. All procedures were completed without any complications.

Definition of terms

The definitions for Ant. and Ret. conduction times and refractory periods have been published. For the present study, the following additional measurements were made. The interval between the Ant. His (H) bundle potential and the subsequent atrial echo response (H Ae interval) during PSVT was measured both from the onset and the end of H to the onset of low right atrial deflection on the His bundle electrogram (HBE) recording. Similarly, the following Ae H interval was measured from the onset of respective deflections. The onset of the low right atrial electrogram during the Ae or PSVT was relatively easy to identify when the Ae coincided, preceded, or clearly followed the ventricular electrogram as occurred in 16 out of 20 patients. In the remaining four patients, the onset of Ae on the HBE was obscured by the ventricular electrogram and the H Ae interval had to be measured indirectly. In these cases the H Ae interval was measured from the H to the onset of the high

Table II

Pt no	Cycle length PSVT (Ae Ae) interval (msec)		H Ae interval (msec)		Range of Ae H interval (msec)	H Ae Ae H	Retrograde H A interval corrected for rate of PSVT		Termination PSVT
	Range	Av	Onset H	End H			End H	Onset H	
Group I									
1	465 535	490	55	30	410-480	1 7 4 8 7	70	90	Ant block
2	260-335	285	65	50	195 270	1 3 0 3 8	82	100	Ant block
3	430-450	440	80 85	60 65	345 365	1 4 2 4 5	100	110	Ant block
4	325 375	340	40	25	285 335	1 7 1 8 3	65	80	Ant block
5	335 390	360	55	35	280 335	1 5 0 6 0	60	80	Ant block
6	580	580	30	20	550	1 17 3	40	60	Ant block
7	450	450	45	20	405	1 9	55	70	Ant & ret block
8	330-340	335	60	60	250 260	1 3 1 3 2	115	130	Ant block
9	390 420	405	50	35	340 370	1 6 8 7 4	65	80	Ant block
10	470 550	515	35	15	445 515	1 12 7 14 7	45	60	Ant block
11	395 415	405	55	35	340 360	1 6 1 6 5	60	60	Ret block
12	475 500	490	40	25	435 460	1 10 8 11 5	45	60	Ant block
13	345 390	370	50	35	295 340	1 5 9 6 8	70	90	Ant block
Group II									
14	460 480	470	200	185	260 280	1 1.3 1 4	–	–	Ant block AVN
15	370 400	385	150	130	220 250	1 1 5 1 7	–	–	Ant block AVN
16	280-370	325	145	125	135 225	1 1 0 1 5	–	–	Ant block AVN
17	270-350	310	175	155	95 175	1 0 5 1 0	–	–	Ant block HPS
Group III									
18	480-570	555	440 470	420 450	100 140	1 0 2 0 3	170-190	190-210	Ret block
19	370-435	405	270-335	255 320	100	1 0 3 0 4	65	85	Ret block
20	410 470	435	300-360	280 350	110	1 0 3 0 4	90	110	Ret block

right atrial electrogram and the interval between the low and high right atrial electrogram as determined during Ret refractory period studies was deducted from the above value The accuracy of such measurements was considered valid only if the sequence of Ret atrial activation during PSVT and Ret refractory period studies was the same and there was no evidence of intra atrial conduction delay, which was the case in all patients

Results

The essential data are summarized in Tables I to III Patients with ventricular pre excitation (Wolff Parkinson White Syndrome) were excluded At the time of study all patients were in sinus rhythm and had not been taking any cardioactive medication for a period of 7 days All patients had documented episodes of PSVT The reentrant nature of the arrhythmia was suggested by the ability to initiate and terminate the PSVT with properly timed atrial premature beats

For all episodes of tachycardia the interval from the onset of H to the onset of Ae (H Ae interval) was measured and correlated with the Ae to subsequent H interval Analysis of the H Ae and Ae H intervals and their ratios (i e H Ae Ae H) permitted classification of patients into three groups

In group I (13 patients nos 1 to 13 Tables I to III) the H Ae and Ae H intervals averaged 52.5 and 366 1 msec respectively (range 30 to 85 msec and 195 to 550 msec respectively) The H Ae Ae H interval ratios were 1 3 1 17 3 Thus for all episodes of PSVT the H Ae values were relatively short compared to the Ae H values

In Group II (four patients, Nos 14 to 17 Tables I to III) the H Ae intervals averaged 167 5 msec (range 145 to 200 msec) whereas the Ae H intervals had an average value of 203 7 msec (range 95 to 280 msec) The H Ae Ae H were 1 0 5 1 7 In Group II the H Ae intervals were relatively longer and the Ae H intervals relatively shorter than in Group I

In Group III (three patients Nos 18 to 20 Tables I III) the H Ae and Ae H interval

Table III Refractory period data

Pt no	Cycle length A,A or V V (msec)	Echo or PSVT one A,A (msec)	Critical range A,H intervals (msec)	Antegrade: Effective refractory period A	AVN	HPS	Antegrade: Functional refractory period AVN	HPS	AVCS	Retrograde: Effective refractory period V	AVN	HPS	Retrograde: Functional refractory period AVN	HPS	VACS
Group I															
1	800	460-400	305-365	320	390	–	615	< 675	6 5	285	–	340	–	515	460
2	500	265-210	210-245	200	–	–	360	< 360	360	210	–	–	–	410	360
3	00	340-310	280-385	290		–	450	< 450	450	230	–	–	–	< 500	380
4	00	360- 40	245-290	230		–	415	< 415	415	210	–	310	–	510	430
5	600	290-280	260-310	260	2 0	–	390	< 390	390	240	–	–	–	440	375
6	800	420	270	280	410	–	485	< 485	485	250	–	–	–	515	440
7	800	410-340	335-465	300	–	–	645	< 645	645	250	–	–	–	460	375
8	00	200-240	180-190	190	–	–	340	< 340	340	260	–	–	–	490	430
9	600	340-290	2 5-340	280	–	–	460	< 460	460	230	–	–	–	440	350
10	1000	600-310	300-550	300	–	–	580	< 580	580	240	–	–	–	< 480	380
11	600	305-290	395-460	260	280	–	430	< 430	430	250	490	–	4 5	465	475
12	600	460-330	300-400	2 0	370	–	540	< 540	540	240	–	–	–	440	370
13	550	390-300	245- 90	230	–	–	450	< 450	450	210	–	–	–	395	365
Group II															
14	00	410-360	190-230	270	350	–	460	< 460	460	310	–	–	–	–	350
15	700	400-300	200-250	290	–	–	450	< 450	450	260	–	–	–	520	275
16	550	420-250	145-200	210	–	–	400	< 400	400	230	–	260	–	460	270
1	600	290-230	95-130	220	–	350	305	330	330	230	–	–	–	430	320
Group III															
18	800	610- 40	100-300	230	–	–	410	< 410	410	220	–	–	545	600	545
19	600	290-230	150-205	220	–	–	3 0	< 3 0	370	250	–	–	–	< 440	320
20	600	330- 60	90-250	250	–	–	360	3 0	3 0	210	–	–	–	470	400

measurements and their ratios were the reverse of Group I The H Ae intervals averaged 362 6 msec (range 270 to 470 msec) and the Ae H intervals were correspondingly short (average 110 msec range 100 to 140 msec) the H Ae Ae H ratios being 1 0 2-0 4

The above classification is schematically presented in Fig 1 and its importance and usefulness will be discussed subsequently

The characteristic electrophysiological features of the three groups will be presented in greater detail as follows

A Characteristic features of PSVT *Group I (patients nos 1 to 13 Tables I to III)* The most prominent and constant features of PSVT in Group I was the short H Ae and long Ae H intervals at all cycle lengths of tachycardia (Fig 2) The Ae response (Ret P wave) was partially or completely obscured by the QRS complex or the initial part of the ST segment In no patient did the onset of Ae precede the H or follow the end of ventricular electrogram on the HBE The H Ae were ≤ H V intervals in nine out of 13 patients and exceeded the latter in the remaining four patients (Tables I and III)[1] The H Ae intervals in Group I remained relatively constant (variations of ≤ 5 msec) with changes in cycle length of PSVT The H Ae Ae H ratios suggested considerably longer Ant conduction times (Ae H) compared to Ret conduction times (H Ae) It may be pointed out that since the point of turn around for the reentrant impulse is proximal to the H bundle the H Ae and Ae H values do not precisely reflect Ant and Ret A V nodal conduction times Changes in the cycle length of PSVT were due to Ae H interval variation the H Ae intervals rarely showed any discernible change Thus the H Ae Ae H ratio increased at longer and decreased at shorter cycle length of tachycardia The shortest Ae H were at least three times longer than H Ae intervals in the same patient at any given time during PSVT Spontaneous or vagotonic (carotid sinus pressure etc) termination of PSVT occurred in the Ant limb of the reentrant circuit (i e the Ae was not followed by an H in 11 out of 13 patients (Fig 2)

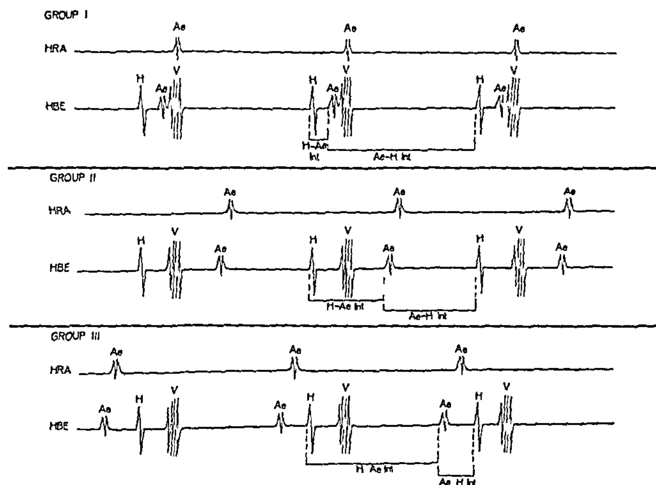


Fig 1 Schematic presentation of patterns of PSVT The figure displays in a schematic fashion the H Ae and Ae H relationship during the tachycardia in the three groups Note the short H Ae and significantly long Ae H intervals in Group I The H Ae and Ae H intervals in Group II approximate each other whereas in Group III the above relationship is just the opposite of Group I The figure also demonstrates the manner in which the above intervals were measured This schema is not representative of the absolute values for any of the given intervals or precise sequence of atrial activation in any of the groups *HRA* = high right atrial electrogram recording *HBE* = His bundle electrogram recording *H* = His bundle deflection *Ae* = atrial echo beat *V* = local ventricular electrogram *Int* = interval The same abbreviations will be used in subsequent figures

and in the Ret limb (i e no Ae following the H) in one patient (No 11) In the remaining one patient (No 7) termination of PSVT occurred in either the Ant or Ret limb Termination of PSVT in the Ant limb was preceded by prolongation shortening or no detectable change in the Ae H interval (Fig 2) In no instance did a PSVT persist when Ant block occurred proximal to the bundle of His (i e in the A V node) On the other hand the development of bundle branch block (seven patients) prolongation in the His Purkinje conduction time (H V interval five patients) or complete block (four patients) within the His Purkinje system (HPS) during a PSVT had no influence on the Ae Ae interval or the H Ae intervals

Whereas single atrial premature beats terminated or reinitiated a PSVT in 12 out of 13 patients single ventricular premature beats terminated the PSVT in only two patients In the 11 out of 13 patients single induced ventricular premature beats to the point of ventricular muscle refractoriness had no effect on the Ae Ae cycle

Group II (patients Nos 11 to 17 Tables I to III) A consistent feature during PSVT in Group II was the relatively long H Ae intervals which caused the Ae to occur after the ventricular electrogram on the HBE tracing (Fig 3 *panel A*) The Ae H intervals were correspondingly short Group II patients were clearly distinguishable from Group I by the smaller H Ae Ae H ratios observed in the latter group (Table II) When a change in the cycle length of PSVT with normal intraventricular conduction was noted in Group II the H Ae (also V Ae) intervals

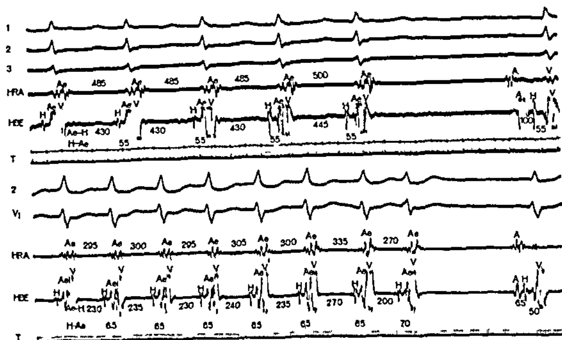


Fig 2 Pattern of PSVT (Group I) The two tracings taken from patients No 1 *(top panel)* and No 2 *(bottom panel)* show the H Ae and Ae H relationship in Group I cases. *In the top panel* the PSVT terminates with subtle increase in Ae-H interval whereas the H Ae stays constant at 55 msec *The bottom panel* shows spontaneous variation in the cycle length of the PSVT primarily from changes in the Ae H intervals The termination of PSVT is preceded by marked shortening in the Ae-H interval which is associated with only 5 msec increase in the H Ae interval Note that the onset of Ae on HBE either precedes local V electrogram *(top panel)* or is obscured by it *(bottom panel)* In both cases the PSVT terminates in the Ant limb (i e no H deflection after the Ae response) Sinus escape beats follow The A H and H V intervals are labelled All measurements are in milliseconds Additional abbreviations 1 2, 3 V = EGC leads *T* = Time lines recorded at 10 and 100 msec pts = patients

remained constant and a change in the Ae H interval accounted for the variation as seen in Group I patients

However unlike Group I abnormal intraventricular conduction during PSVT had a pronounced influence on the atrial cycle length of tachycardia in Group II cases In three patients functional bundle branch block resulted in an increase in H Ae interval and consequently the cycle length of PSVT (Ae Ae interval) An H Ae interval prolongation during bundle branch block pattern was due to an increase in the V Ae interval and also the H V interval when the latter coexisted confirming that the pattern of ventricular muscle activation influenced the subsequent Ae response (Fig 3 *panels B and C*)

In all Group II cases PSVT terminated in the Ant limb with block of the Ae proximal to the H in three and distal to the H in the fourth patient (No 7 Fig 3 *panel B*) Appropriately timed single atrial and ventricular premature beats terminated or reinitiated the PSVT in all four patients In three out of four patients single premature ventricular beats induced coincident with or following the H during PSVT resulted in Ret atrial capture (Ar) ahead of the expected Ae response (i.e the Ae Ar < Ae Ae Fig *4 panel C*) In one patient the premature ventricular beat delivered in the above manner terminated the PSVT without propagation to the atria

Group III (patients Nos 18 to 20 Table I to III) In Group III the H Ae Ae H ratios were the reverse of Group I (Fig 5 *panels B* and *C*) A change in the cycle length of the PSVT was due to changes in the H Ae in two and both H Ae and Ae H interval in one patient Spontaneous termination of PSVT always occurred in the Ret limb (i.e H was not followed by an Ae (Fig 5 *panel C*) Aberrant ventricular conduction (seen in two out of three patients) appeared to have no effect on the Ae Ae the Ae H or H Ae intervals Single premature atrial beats effectively terminated the PSVT in all patients whereas single premature

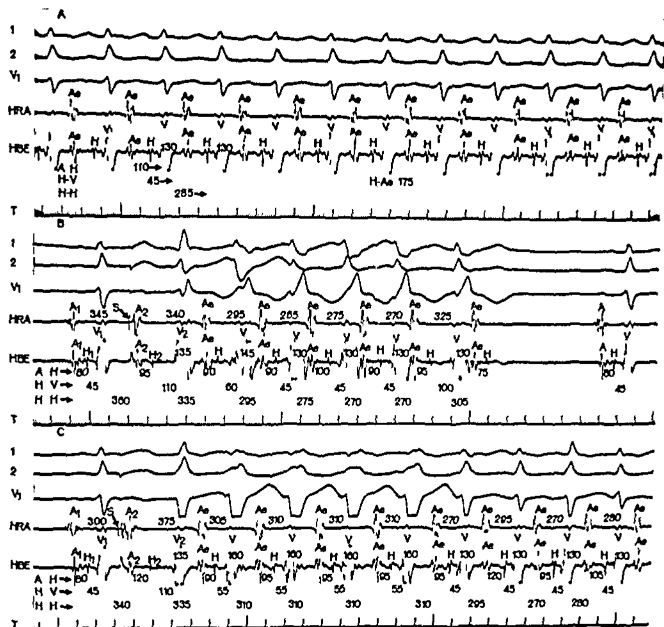


Fig 3 Pattern of PSVT (Group II Patient No 17) The tracing shows the H Ae and Ae H relationship during PSVT in Group II during normal *(panel A)* and aberrant intraventricular conduction *(panels B and C)* *In panel A* the cycle length of PSVT (Ae Ae) is 285 msec the H Ae and Ae H intervals measure 175 and 110 msec respectively a ratio of 1 0 6 The H V and V Ae intervals during normal intraventricular conduction value 45 to 130 msec in that order *Panel B and C* show initiation of PSVT with single premature atrial beats (A) coupled to the preceding sinus beats (A) During RBBB *(panel B)* the V Ae interval is 130 msec (labelled within the V electrogram) and is the same as in panel A whereas during LBBB *(panel C)* the V Ae is prolonged (160 msec) See how the H V prolongation and intraventricular conduction influence the subsequent Ae Also when the impulse *blocks below the bundle of His (panel B) there is no Ae response The prolongation in Ae Ae cycle with H V* prolongation and during LBBB suggest the reentry via a bypass connected to the left ventricle It is to be observed that there is no evidence of ventricular pre-excitation during sinus beat *(last beat in panel B)* Near simultaneous activation of the high and low right atrium during PSVT is also compatible with left sided accessory pathway i e from left ventricle to the left atrium *S* = denotes stimulus artifact RBBB = right bundle branch block *LBBB = left bundle branch block*

ventricular beats terminated the tachycardia in only one

B Antegrade and retrograde conduction patterns *Group I (patients Nos 1 to 13 Table I)* Incremental atrial pacing produced progressive prolongation *in A V nodal conduction (A H inter*val) and in all patients a PSVT could be initiated *during pacing induced Wenckebach phenomenon* when critical A H delays were achieved (Fig 6 *top panel*) [4] The average paced atrial cycle length at the onset of A V nodal Wenckebach phenomenon was 423 4 msec (range 665 to 300 msec) In

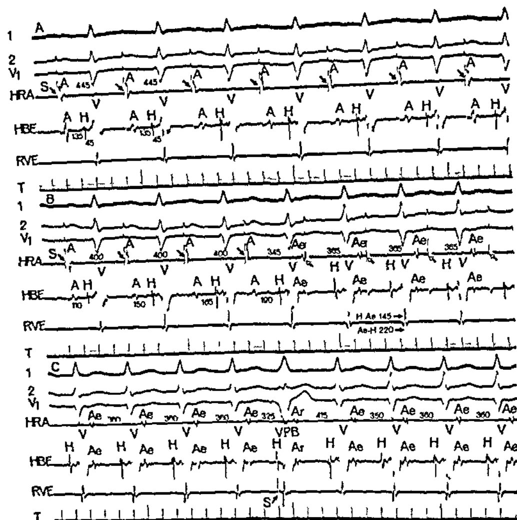


Fig 4 Pattern of PSVT (Group II patient No 16) *Panel A* demonstrates 1:1 A-V response at a paced atrial cycle length of 445 msec The A-H and H-V intervals are 135 and 45 msec respectively There is no evidence of Ant ventricular pre-excitation Shortening of the atrial cycle length to 400 msec *(panel B)* results in Ant A-V nodal WP The fourth paced beat is associated with an A-H of 190 msec which initiates the PSVT The Ae response precedes the next stimulus artifact *(white arrow)* which is ineffective The cycle length of PSVT is 345 to 365 msec The H-Ae and Ae-H intervals are labelled *Panel c* shows that introduction of a ventricular premature beat *(VPB)* during stable PSVT which coincides with the Ant His bundle activation results in Ret atrial capture *(Ar)* ahead of anticipated Ae response i.e. Ae-Ar < Ae-Ae by 35 msec The curtailed atrial cycle *(Ae-Ar)* results in prolongation in the following A-H interval which in turn prolongs the atrial cycle length (Ar-Ae) to 415 msec The V-Ae remains the same as in panel B Subsequently the Ae-Ae intervals stabilize at 360 msec *RVE* = right ventricular electrogram WP = Wenckebach phenomenon

seven out of 13 patients the longest paced atrial cycle length which resulted in A-V nodal Wenckebach phenomenon were longer than the atrial cycle length of the PSVT such that the first Ae preceded the next expected paced impulse (Fig 6) In the remaining six patients the atrial cycle length during a PSVT were equal to or greater than the paced atrial cycle length producing A-V nodal Wenckebach phenomenon

In all Group I patients incremental ventricular pacing produced small but definite increases in V-A intervals At the slowest paced ventricular rates the V-A intervals averaged 137.3 msec (range 115 to 200 msec) The average increase in V-A interval from the longest to the shortest paced ventricular cycle length with 1:1 V-A response was 21.1 msec (range 5 to 70 msec) The V-A intervals prolongation in all probability

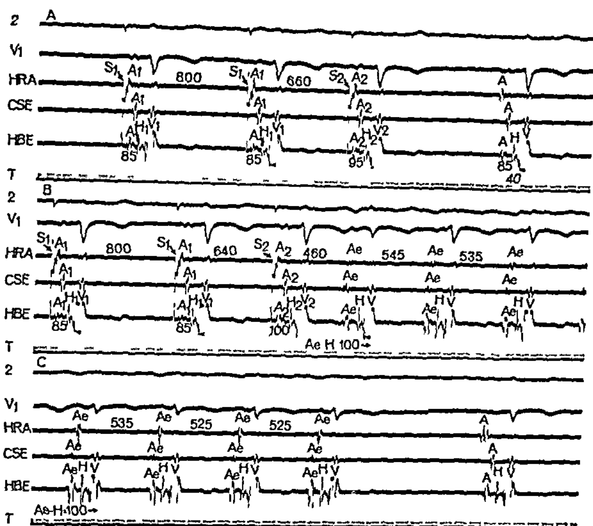


Fig 5 Pattern of PSVT (Group III patient No 18) *Panel B* demonstrates initiation of PSVT with an atrial coupling interval of 640 msec *The A₂H interval in panel B is only slightly longer than the A H interval of the* basic drive beat The PSVT could not be induced at longer coupling intervals and shorter A H delays *(panel A)* Observe the relatively long *H Ae* and correspondingly short *Ae* H interval *(panel B and C) Panel C* shows spontaneous termination of the PSVT in the retrograde limb See text for details *CSE* = coronary sinus electrogram

represented increases in the H A intervals (Ret A V nodal conduction time) rather than the V H interval (Ret HPS conduction time) [11]

In 11 out of 13 patients a 1 1 V A response occurred up to maximum paced ventricular rates (average cycle length 355 4 msec) whereas in two patients Ret block occurred at cycle length of 400 and 460 msec respectively In seven out of 13 patients Ant A V nodal Wenckebach phenomenon occurred at slower paced rates than did Ret Wenckebach phenomenon (Fig 6) In four out of 13 patients 1 1 A V and V A responses occurred up to maximum comparable paced rates Of the remaining two patients who developed both Ant and Ret Wenckebach phenomenon during incremental pacing in only one patient did the onset of Ret Wenckebach phenomenon occur at a slower rate

In only two out of 13 patients could a PSVT be initiated during continuous ventricular pacing and in both no prior prolongation in the V A intervals were noted (Fig 6 bottom panel)

Group II (patients Nos 14 to 17 Table I) In Group II conduction patterns during incremental atrial pacing were similar to Group I The average atrial cycle length at the onset of Ant A V nodal Wenckebach phenomenon was 396 2 msec (range 300 to 460 msec) In all four patients a PSVT could be induced when critical degrees of A H delays were achieved (Fig 4 panels A and B) In two patients the atrial cycle length during PSVT was shorter (Fig 4 panel B) than the paced atrial cycle length which initiated a tachycardia The opposite was observed in the remaining two patients Incremental ventricular pacing produced no increases in V A intervals up

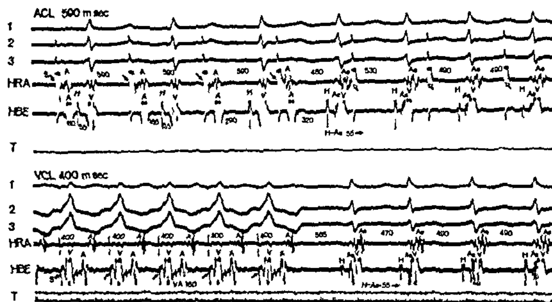


Fig 6 Antegrade and retrograde conduction pattern (Group I patient No 1) *The top panel* shows Ant AV nodal Wenckebach cycle at a paced atrial CL of 590 msec The longest conducted A H interval of 370 msec results in the initiation of PSVT The first Ae response precedes the oncoming artificial stimulus which is ineffective *(white arrow)* The CL of PSVT is significantly shorter than the paced ACL which produced Ant AV nodal WP During ventricular pacing *(bottom panel)* at a CL of 400 msec 1 1 V A response occurs the V A interval measures 160 msec. When the stimulus is omitted following the fifth paced beat the PSVT is initiated without prior prolongation in V A interval. Note that VA conduction system in this patient was capable of sustaining a 1 1 response at faster rates compared to the AV conduction system CL = cycle length ACL = paced atrial cycle length VCL = paced ventricular cycle length WP = Wenckebach phenomenon

to maximum paced rates of 170 to 200 beats/min The V A intervals averaged 136 2 msec (range 110 to 165 msec)

In none of Group II patients was a PSVT induced during incremental ventricular pacing

Group III (patients Nos 18 to 20 Table I) Progressive increases in A H intervals occurred during incremental atrial pacing The average paced atrial cycle length at the onset of Ant A V nodal Wenckebach phenomenon was 348 3 msec (range 315 to 400 msec) In all three patients a PSVT was initiated during incremental atrial pacing However the A H intervals which preceded the onset of PSVT were only slightly longer than those of sinus beats (i.e., 10 to 75 msec > A H intervals of sinus beats) In all patients the atrial cycle length during a PSVT was longer than the paced atrial cycle length resulting in Ant A V nodal Wenckebach phenomenon

The V A intervals at the longest paced ventricular cycle length averaged 150 msec (range 140 to 160 msec) The average increase in V A from slowest to the fastest paced ventricular rates with 1 1 V A response was 21 6 msec (range 10 to 30 msec) In one patient Ret Wenckebach phenomenon occurred at slower paced rates than did the Ant counterpart and in the remaining two patients 1 1 A V and V A responses were observed up to the maximum paced rates In one out of three patients was a PSVT initiated during progressive prolongation in V A intervals produced by ventricular pacing

C Antegrade and retrograde refractory periods Table III lists for the three groups of patients the pertinent refractory period data obtained at comparable atrial and ventricular paced cycle lengths (i.e A_1A_1 or V_1V_1)

Group I Antegrade refractory period studies Within a critical range of A_1A_2 intervals and A_2H_2 delays, A_2 always resulted in PSVT (Fig 7) The longest A_1A_2 and shortest A_2H_2 intervals which initiated PSVT had mean values of 381 5 ± 93 5 and 276 2 ± 55 3 msec., respectively The critical range of A_2H_2 delays were comparable to the critical A H intervals which produced PSVT

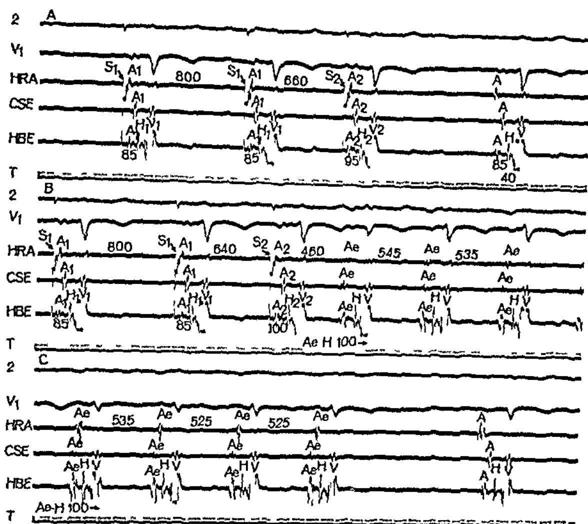


Fig 5 Pattern of PSVT (Group III patient No 18) *Panel B* demonstrates initiation of PSVT with an atrial coupling interval of 640 msec The A,H interval in panel B is only slightly longer than the A H interval of the basic drive beat The PSVT could not be induced at longer coupling intervals and shorter A H delays *(panel A) Observe the relatively long H Ae and correspondingly short Ae H interval (panel B and C) Panel C* shows spontaneous termination of the PSVT in the retrograde limb See text for details CSE = coronary sinus electrogram

represented increases in the H A intervals (Ret A V nodal conduction time) rather than the V H interval (Ret HPS conduction time)[13]

In 11 out of 13 patients a 1 1 V A response occurred up to maximum paced ventricular rates (average cycle length 355 4 msec) whereas in two patients Ret block occurred at cycle length of 400 and 460 msec respectively In seven out of 13 patients Ant A V nodal Wenckebach phenomenon occurred at slower paced rates than did Ret Wenckebach phenomenon (Fig 6) In four out of 13 patients 1 1 A V and V A responses occurred up to maximum comparable paced rates Of the remaining two patients who developed both Ant and Ret Wenckebach phenomenon during incremental pacing in only one patient did the onset of Ret Wenckebach phenomenon occur at a slower rate

In only two out of 13 patients could a PSVT be initiated during continuous ventricular pacing and in both no prior prolongation in the V A intervals were noted *(Fig 6 bottom panel)*

Group II (patients Nos 14 to 17 Table I) In Group II conduction patterns during incremental atrial pacing were similar to Group I The average atrial cycle length at the onset of Ant A V nodal Wenckebach phenomenon was 396 2 msec (range 300 to 460 msec) In all four patients a *PSVT could be induced when critical* degrees of A H delays were achieved (Fig 4 *panels A and B)* In two patients the atrial cycle length during PSVT was shorter (Fig 4 *panel B)* than the paced atrial cycle length which initiated a tachycardia The opposite was observed in the remaining two patients Incremental ventricular pacing produced no increases in V A intervals up

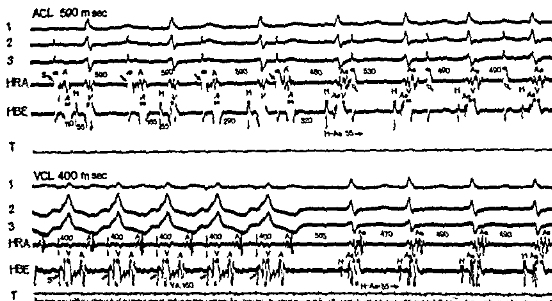


Fig 6 Antegrade and retrograde conduction pattern (Group I patient No 1) *The top panel* shows Ant AV nodal Wenckebach cycle at a paced atrial CL of 590 msec *The longest conducted A H interval of 390 msec results in the initiation of PSVT The first Ae response precedes the oncoming artificial stimulus which is ineffective (white arrow)* The CL of PSVT is significantly shorter than the paced ACL which produced Ant AV nodal WP *During ventricular pacing (bottom panel)* at a CL of 400 msec 1 1 V A response occurs the V A interval measures 160 msec *When the stimulus is omitted following the fifth paced beat the PSVT is initiated without prior prolongation in V A interval.* Note that VA conduction system in this patient was capable of sustaining a 1 1 response at faster rates compared to the AV conduction system *CL = cycle length ACL* = paced atrial cycle length *VCL* = paced ventricular cycle length WP = Wenckebach phenomenon

to maximum paced rates of 170 to 200 beats/min The V A *intervals averaged 136 2* msec (range 110 to 165 msec)

In none of Group II patients was a PSVT induced during incremental ventricular pacing

Group III (patients Nos 18 to 20 Table I) Progressive increases in A H intervals occurred during incremental atrial pacing The average paced atrial cycle length at the onset of Ant A V nodal Wenckebach phenomenon was 348 3 msec (range 315 to 400 msec) *In all three patients a* PSVT was initiated during incremental atrial pacing However the A H *intervals* which preceded the onset of PSVT were only slightly *longer than those of* sinus beats (i e 10 to 75 msec > A H intervals of sinus beats) *In all patients the atrial cycle length* during a PSVT was longer than the paced atrial cycle length resulting in Ant A V nodal Wenckebach phenomenon

The V A *intervals* at the longest paced ventricular cycle length averaged 150 msec *(range 140 to 160* msec) The average increase in V A from slowest to the fastest paced ventricular rates with 1 1 V A *response* was 21 6 msec (range 10 to 30 msec) In one patient Ret Wenckebach phenomenon occurred at slower paced rates than did the Ant counterpart and in the remaining two patients 1 1 A V and V A responses were observed up to the maximum paced rates In one out of three patients was a PSVT initiated during progressive prolongation in V A intervals produced by ventricular pacing

C Antegrade and retrograde refractory periods Table III lists for the three *groups of* patients the pertinent refractory period data obtained at comparable atrial and *ventricular* paced cycle lengths (i e A_1A or V V)

Group I Antegrade refractory period studies Within a critical range of A A_2 intervals and A_2H_2 delays A_2 always resulted in PSVT (Fig 7) The longest A A_2 and shortest A H_2 intervals which *initiated* PSVT had mean values of 381 5 ± 93 5 and 276 2 ± 55 3 msec respectively The critical range of A H delays were comparable to the critical A H intervals which produced PSVT

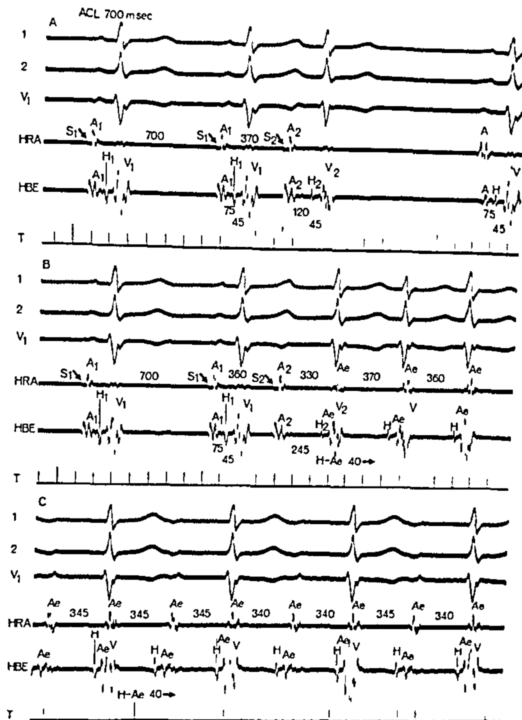


Fig 7 Antegrade refractory period pattern (Group I patient No 4) At a basic atrial cycle length of 700 an A_1A_2 of 370 msec A_2 conducts with an A_2H_2 of 120 and an H_2V_2 of 45 msec respectively The resulting H_1H_2 interval was the shortest obtainable at this CL and measures 415 msec (FRP AV node) Since no prolongation in HV interval was noted during premature beat the H_1H_2 equal V_1V_2 such that the FRP of the AVCS is determined by the AV node *Panel B* shows initiation of PSVT at closer A_1A_2 interval of 360 msec Sudden prolongation of A_2H_2 interval occurs and coincides with beginning of the PSVT Discontinuous FRP curves were noted in this patient (ref 7) The typical H Ae and Ae H relationship of Group I patients is obvious An episode of 2 1 block within the HPS is shown in *panel C* during PSVT and it should be noted that the H Ae and Ae H relationship remains the same as in panel B The onset of Ae on HBE is clearly identifiable when there is no accompanying local ventricular electrogram *(panel C)*

during incremental atrial pacing In ten out of thirteen patients the atrial cycle length during incremental pacing which resulted in PSVT exceeded the A_1A_2 intervals which initiated the tachycardia The Ant effective refractory period (ERP) of the A V node was longer than atrial ERP in five patients whereas the latter exceeded the former in the remaining eight patients Neither Ae nor PSVT were noted when A_2 blocked proximal to the bundle of His

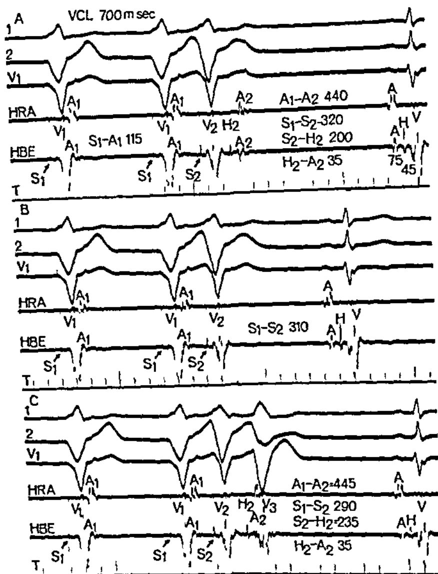


Fig 8 Retrograde refractory period pattern (Group I patient No 4) The basic ventricular cycle length (S S) is constant at 700 msec in all panels. The retrograde His bundle deflection during the basic drive is obscured by the local ventricular electrogram At an S S interval of 320 msec *(panel A)* the S conducts to the atria with S H (Ret His-Purkinje conduction time) of 200 msec and an H,A (Ret. AV nodal conduction time) of 35 msec A sinus escape beat follows. At a closer S S of 310 msec *(panel B)* S blocks below the bundle of His. Further decrease in S S interval *(panel C)* results in resumption of V A conduction and V is followed by another reentrant ventricular beat (V) from reentry within the HPS The V fails to retrogradely depolarize the atria (i.e., no A) by virtue of its block below the bundle of His. Note that the H,A intervals in *panels A* and *C* measure the same and the shortest A A (FRP VACS, *panel A*) is determined primarily by the HPS Also evident is the fact that PSVT was not initiated during premature ventricular stimulation either by V or V_3.

During Ant refractory period studies the functional refractory period (FRP) of the A V node exceeded the FRP ERP and relative refractory period of the HPS Therefore the FRP of the atrioventricular conduction system (AVCS) was determined by the A V node in all patients (i e shortest H H, equaled the shortest V V intervals [Fig 7 *top panel*]) Three patients (Nos 4 12 and 14) demonstrated discontinuous curves during refractory period measurements similar to those described previously [1]

Retrograde refractory period studies During Ret refractory period determinations the HPS had the longest ERP in two patients the

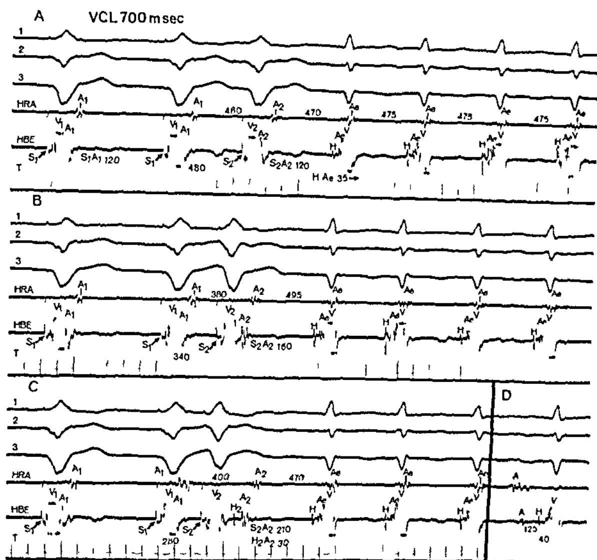


Fig 9 Retrograde refractory period pattern (Group I patient No 10) The figure demonstrates initiation of PSVT at a basic ventricular cycle length of 700 msec and at decreasing S S intervals *(Panels A to C) In panel A* the PSVT starts at an S S of 480 msec without any discernible prolongation in the V A interval i e S A = S A The *PSVT could be initiated at all shorter S S intervals Panel C demonstrates emergence of H from V Note the* relatively short H A interval of 30 msec *Panel D* shows a reference sinus beat

A V node in one patient and the ventricular muscle in ten patients The FRP of the ventriculo atrial conduction system (VACS) was determined by the HPS in 12 out of 13 patients (i e Ret delay was only encountered below the bundle of His Fig 8) and the A V node in one patient The FRP of the AVCS was significantly longer than that of the VACS in Group I (FRP AVCS 478 ± 104 0 msec FRP VACS 393 4 ± 34 7 msec p value < 0 025)

In five out of 13 patients the induced premature ventricular beat (V) was followed by a reentrant beat (V) resulting from reentry within the HPS In none of these patients did V_3 conduct to the atria nor did V_2 or V_3 initiate a PSVT (Fig 8 *bottom panel)* In only one patient from Group I did V initiate the PSVT (Fig 9)

During Ret refractory period studies the Ret H bundle deflection during the basic drive (H_1) was obscured by the ventricular electrogram However at closer V_1V intervals the Ret H emerged from V_2 in all patients In 12 out of 13 patients the H A_2 intervals were noted to remain constant at decreasing V_1V_2 intervals The H A_2 intervals (as measured from the end of H_2 to the onset of A_2) in Group I patients averaged 47 7 msec (range 25 to 80 msec) An attempt was made to compare the Ret H A with H Ae interval measured from comparable points i e from the end of H during Ret and from the onset of H during Ant depolarization of the His bundle Since the H A intervals were determined during refractory period studies and were preceded by longer intervals compared to the cycle length of PSVT (i e the Ret H_1H_2 were > H H cycle of PSVT) the H A intervals were not directly

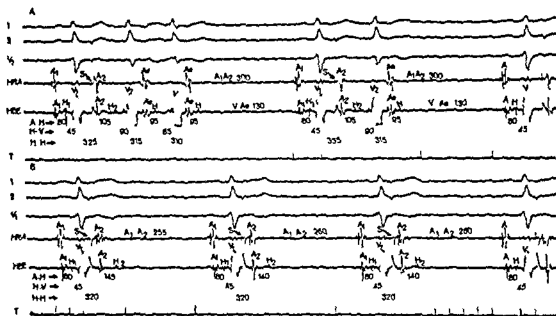


Fig 10 Initiation and spontaneous termination of PSVT (Group II patient No 17) Premature atrial beats (A₂) are coupled to preceding sinus beats (A₁) Initiation of PSVT is shown in *panel A* where A₂ conducts with A₂H₂ of 105 msec and H₂V₂ of 90 msec Note the spontaneous termination of tachycardia when the impulse antegradely blocks below the bundle of His. The Ae H interval of the last two beats in the first episode *(panel A) measures the same and the Ae* response only occurs when the reentrant impulse activates the ventricles This is clearly shown also in *panel B* where A₂H₂ delays are longer compared to panel A however in the absence of ventricular activation the PSVT is not initiated.

comparable to the H Ae intervals and therefore the H A intervals were corrected for the rate of PSVT in the following manner Since the H A intervals during slow ventricular paced rates were equal to or less than H A intervals *in any given* patient *the increment of V A intervals* from the slow ventricular rates to the ventricular rates similar to the rate of PSVT were added to the H A values These correct H A values so obtained cannot be considered precise but should only slightly exceed if at all the true H A intervals if the latter could be directly measured When the corrected H A intervals were compared to the H Ae intervals *the former exceeded the* latter by an average of 20 msec (range 5 to 70 msec) or less in Group I patients.

Group II Antegrade refractory period studies The critical A A intervals which induced PSVT in Group II were similar to group I (351.5 ± 93.5 msec for Group I vs 380 ± 60.? msec for Group II) but the minimum A H intervals necessary to initiate a PSVT were considerably shorter for Group II cases (161.2 ± 41.8 vs 2?6.2 ± 5?.3 msec, p value < 0.01) Since ventricular muscle appeared to be essential for the occurrence of PSVT in these patients it is obvious that the critical intervals were the A V (i e A H + H V) rather than A H intervals In three out of four patients the A_2H prolongation was *not accompanied by* H_2V_2 prolongation and therefore increases in A_2V_2 intervals paralleled *that of the* AH_2 intervals However in one patient who did *demonstrate* HV_2 prolongation during atrial premature stimulation *it could be* directly documented that the initiation of PSVT required critical A V rather than A H delays (Fig 10)

In one patient the A V node and in one patient *the HPS* had the longest ERP during Ant refractory period studies In the remaining two patients *the atrial ERP* exceeded the FRP of the A V node and the HPS The FRP of the AVCS was *determined* by the A V node in three patients and by the HPS in one patient

Retrograde refractory period studies During Ret refractory period studies V_2A_2 equaled the V_1A at decreasing V V_2 *intervals* At closer coupling intervals when H emerged from the ventricular electrogram the Ret A_2 *preceded* H_2 (Figs 11 and 12) suggesting conduction via an

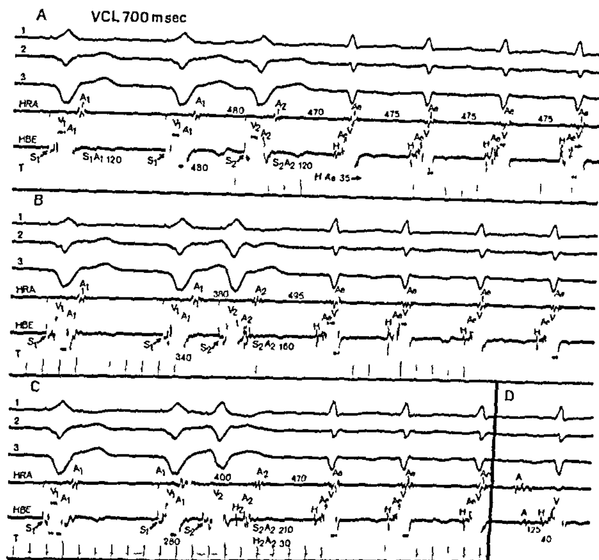


Fig 9 Retrograde refractory period pattern (Group I patient No 10) The figure demonstrates initiation of PSVT at a basic ventricular cycle length of 700 msec and at decreasing S S intervals (panels A to C) In panel A the PSVT starts at an S S_2 of 480 msec without any discernible prolongation in the V A interval i e S A = S A The PSVT could be initiated at all shorter S S intervals *Panel C* demonstrates emergence of H from V Note the *relatively short H_2A interval of 30 msec Panel D shows a reference sinus beat*

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During Ret refractory period studies the Ret H bundle deflection during the basic drive (*H_1*) was obscured by the ventricular electrogram However at closer V_1V_2 *intervals* the Ret H emerged from V_2 in all patients In 12 out of 13 patients the H A_2 intervals were noted to remain constant at decreasing V_1V intervals The H A intervals (as measured from *the end of H to the onset of A_2) in Group I patients averaged* 47 7 msec (range 25 to 80 msec) An attempt was made to compare the Ret H A with H Ae interval measured from comparable points i e from the end of H *during Ret and from the onset* of H during Ant depolarization of the His bundle Since the H A intervals were determined during refractory period studies and were preceded by longer intervals compared *to the cycle length of* PSVT (*i e the Ret H_1H_2 were* > H H cycle of PSVT) the H A_2 intervals were not directly

which A antegradely conducted over the normal pathway to initiate a PSVT (Fig 12) * When V failed to activate the atria (A_1) the PSVT did not occur (one out of three patients (Fig 11 *top panel*)

Group III Antegrade refractory period studies The echo and PSVT zone in Group III was quite comparable to the other two groups However the shortest A H delays which produced PSVT in Group III were significantly shorter (Fig 5 *panels A* and *B*) than in Group I patients (113 3 ± 32 1 msec vs 276 2 ± 3 msec p value < 0 001) No statistically significant difference existed between Group II and III patients when the above comparisons were made The atrial muscle had the longest ERP in all three patients and the FRP of the AVCS was determined by the A V node in two patients and the HPS in one patient

Retrograde refractory period studies During Ret refractory period studies the FRP of the ventricular muscle exceeded that of the A V node and HPS in all three patients

The FRP of the VACS was determined by the A V node in one patient and the HPS in the other two patients The mean value for the FRP of the VACS was 421 6 ± 114 and AVCS 383 3 ± 23 msec the differences however were statistically insignificant

The PSVT could be initiated with a single ventricular premature beat in only one patient The ventricular premature beats that initiated PSVT were associated with V A_1 intervals that were longer than V A intervals

For the entire group of 20 patients the mean value for the atrial ERP exceeded that of the ventricular ERP but no significant difference was noted Similarly there was no significant difference between the atrial and ventricular ERP between the three groups

Discussion

It is apparent from the present study and previous reports that the site of reentry in patients with PSVT in the absence of ventricular pre-excitation is variable and an attempt should be made to delineate the reentrant circuits in individual patients The present data indicates that in Group I patients (which constituted the majority) the most likely site of reentry was the A V node whereas in Group II patients a Ret AP of the Kent bundle type was utilized by the reentrant impulse during PSVT

In Group III patients although a limited number of observations were available it was possible to exclude the utilization of a Ret AP during PSVT Whether the site of reentry in Group III patients was the A V node or the low atria will be discussed subsequently

It is important to emphasize that certain electrophysiological findings were of no help in determining the site of reentry in this series of patients These include resting ECG P R intervals cycle length of PSVT initiation of PSVT with single premature atrial beats or during Ant A V nodal Wenckebach phenomenon The role of those electrophysiologic parameters which allowed localization of the reentrant pathways along with their limitation are discussed below

1 Effect of abnormal intraventricular conduction on cycle length of PSVT A change in cycle length of PSVT during a change in intraventricular conduction suggests reentry via an AP Since ventricular muscle activation is an essential link in the reentrant circuit in such cases (Group II) both H V prolongation and ipsilateral bundle branch block (on the side of AP connection) during PSVT will prolong the H Ae and V Ae intervals (Fig 3) The Ae Ae prolongation at times however is followed by a significantly shorter Ae H interval and if such a conduction pattern stablizes the cycle length of PSVT during aberrant conduction may in fact, be shorter than during normal intraventricular conduction The reverse may occur when abnormal intraventricular conduction converts to normal conduction during a PSVT retrogradely utilizing an AP The sudden decrease in Ae Ae cycle may either result in Ae H prolongation and consequent increase in the atrial cycle length of PSVT (Fig 13) or the Ae may block antegradely and terminate the PSVT It is important therefore that Ae Ae intervals be analyzed at the transition in intraventricular conduction since during established normal or abnormal intraventricular conduction the cycle length of PSVT may be the same even though the H Ae intervals stay longer during aberrant ventricular conduction

2 Effect of single ventricular premature beats on cycle length of PSVT During PSVT if single ventricular premature beats induced coincident with or following the Ant H result in termination of PSVT or in Ret atrial capture (Ar) sooner than the expected Ae reentry via a Ret AP is strongly suggested The above criterion is still

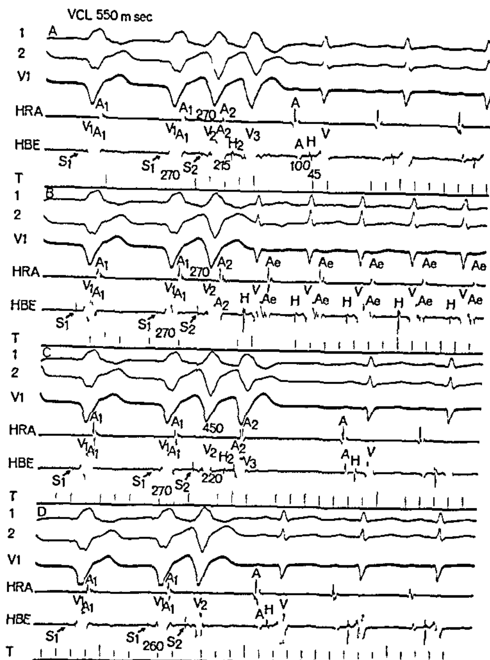


Fig 11 Retrograde refractory period pattern in PSVT (Group II patient No 16) In all panels the ba ic ventricular cycle length is the same *In panel A* S_2 *conducts retrogradely with an S A, interval which equals to* S A such that the A A = S S The S also conducts to the bundle of His with an S H interval of 215 msec Another ventricular beat from reentry in the HPS (V) follows The fact that the A_2 precedes H suggests that atrial activation occurred via an accessory pathway not connected *to the bundle of His (Kent bundle)* V_3 blocks retrogradely in both pathways and a sinus beat follows *In panel B* the S retrogradely blocks below the bundle of His (no H) however S conducts to the atria (A) via the accessory pathway A in turn conducts antegradely via the normal pathway and the PSVT is initiated *In panel C* the S blocks retrogradely in the accessory pathway and conducts via the normal pathway (H precedes A) The V response occurs from S H delay similar to the one seen *in panel A* The S S intervals *in panels A to C* are the same *At a shorter coupling interval of 260 msec (panel D)* S_2 blocks retrogradely in both pathways (no H or A) The shortest A A intervals were achieved by conduction via a Kent bundle silent antegradely (see the sinus beats and *compare with those during PSVT)* so that the FRI of the VACS was determined by refractoriness of the bypass tract

accessory pathway not in direct continuity with the bundle of His In only one patient did the Ret *ERP of the acessory pathway (AP) exceed that of* the ventricular muscle (Fig 11) whereas *in the* remaining three patients the Ret ERP of the AP was less than that of the ventricular muscle The FRP of the VACS in Group II (which was determined by the AP) was *significantly shorter* than FRP of the AVCS (p value < 0 001) In *three out of four patients closer* V_1V_2 *intervals resulted in* V_3 from reentry in the HPS In two out of three patients V_2 retrogradely blocked below the bundle of His (i e no H_2) while conducting to the atria (A_2) via the AP following

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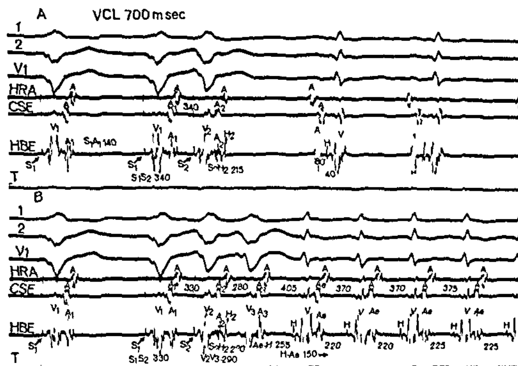


Fig 12 Retrograde refractory period pattern (Group II patient No 15) At a basic ventricular cycle length of 700 msec and an S S_2 of 340 msec *(Panel A)* A_2 response occurs via an accessory pathway S also conducts to the bundle of His with an S H_2 of 215 msec *Note the absence of ventricular pre-excitation during sinus beat At shorter* S S_2 and longer S_2H_2 delay *(panel B)* V_2 is followed by another ventricular beat (V_3) from reentry within the HPS V_3 in turn activates the atria (A) via the anomalous pathway and at the same time blocks below the bundle of His A_3 finds the normal pathway recovered sufficiently and antegradely conducts to start the tachycardia

valid if the induced beat precedes the Ant H by an interval less than the H V intervals of sinus beats *since the V H interval (during right* ventricular apical pacing) almost always exceeds the H V interval[13] However if the premature ventricular beat precedes the Ant H by more than the H V interval of sinus beats, then it is theoretically possible to engage the Ret limb of an A V nodal reentry circuit which will make it difficult to determine whether the reentry is occurring within the A V node or via an AP It was however noted in this study that single ventricular premature beats rarely had any effect in Group I and III patients whereas the PSVT *was uniformly terminated in Group II patients* The lack of effect of single premature ventricular beats may be due to either (a) that the reentry circuits in Groups I and III were located farther away from the site of stimulation (i e the A V node or atrium) and/or (b) the premature ventricular beats blocked retrogradely below the bundle of His which will obviously have no effect upon the reentry in or above the A V node but could still engage a Kent bundle

3 Antegrade and retrograde conduction ratios during PSVT A relatively simple and reproducible finding which suggested the site of reentry was the H Ae and Ae H relationship Neither the H Ae intervals nor the H Ae Ae H showed any overlap of values between the three groups in this *series of patients*

In Group I in whom the site of reentry was the A V node the Ae had a constant relationship with the H over a wide range of PSVT rates and the Ae never preceded the H or followed the end *of ventricular electrogram in HBE recording* If functional and/or anatomic duality of A V nodal pathways is the basis of reentry in *these patients* then it is conceivable that *Ant block in one* pathway with prolonged conduction (A H interval) in the other pathway may allow good conduction in the Ret limb of reentry circuit and *account for the short H Ae intervals* The short H Ae in turn will be followed by longer Ae H interval and if such a conduction is *stabilized the* pattern of Group I PSVT will *emerge Theoreti*cally conduction in Ant and Ret limbs of A V nodal reentry circuit could balance such that the H Ae and Ae H intervals may approximate each *other (pattern of Group II)* or the H Ae may exceed the Ae H interval (pattern of Group III) This *however did not occur in any of the* patients in Group I at any time

The presence of relatively *longer H Ae inter*vals during PSVT in Group II patients was not surprising since the H Ae intervals included

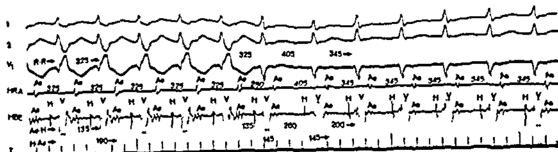


Fig 13 Intraventricular conduction and rate of PSVT (Group II patient No 16) The cycle length of PSVT is initially stable at 325 msec during aberrant intraventricular conduction of the right bundle branch block type The Ae H and H Ae intervals measure 135 and 190 msec respectively With the conversion of intraventricular conduction to normal (sixth QRS complex) there is sudden decrease in H Ae interval to 145 msec which results in corresponding shortening of the Ae Ae interval The decrease in the Ae Ae cycle length to 280 msec results in *significant prolongation in the following Ae H interval which measures 260 msec* and by virtue of which both Ae Ae and R R intervals increase to a value of 405 msec Subsequently the conduction stabilizes such that the cycle length of PSVT during normal QRS complex is longer than during aberrant QRS complexes The H V interval *throughout the episode of PSVT is the same (i.e., 45 msec)* and therefore the decrease in the H Ae during normal intraventricular conduction is entirely accounted for by a decrease in V Ae interval which suggests a right sided ventriculoatrial bypass connection

conduction times (1) in the HPS (the H V interval) (2) from the onset of ventricular activation to the Ret penetration of the AP (3) within the AP and (4) to the atrium in the vicinity of HBE recording site It is to be noted that since most anomalous connection of the Kent bundle type are located around the base of the heart (i e A V ring) a significant amount of time may elapse between the ventricle activation via the normal pathway and Ret penetration of the AP This is probably true for both patients with or without evidence of Ant ventricular pre excitation (the delta wave) One can argue that if an atrial recording was made in closer proximity to the *atrial end of the AP* the H Ae (where the Ae is recorded from an atrial site close to the AP) will be shorter Although this is true the Ae as recorded on the HBE usually occurs late enough to be clearly separated from the ventricular electrogram regardless of the atrial and ventricular end of the bypass insertion Patients with septal connections may have shorter H Ae and V Ae intervals compared to those with more lateral connection However the H Ae and Ae H interval relationship presented here for Group II cases appears to be the rule rather than the exception in patients with WPW syndrome in whom reentry via a bypass was documented with epicardial mapping technique The ratios presented in Table II were obtained during normal intraventricular conduction and it goes without saying that abnormal intraventricular conduction during PSVT in these cases may significantly change these ratios

In group III patients the PSVT was initiated at relatively shorter A H_2 intervals compared to Group I patients and H Ae intervals were correspondingly longer Although reentry via an AP was excluded the exact site of reentry was difficult to determine in Group III patients due to limited number of observations available The reversal of H Ae Ae H may conceivably reflect reversal of conduction balance or direction of conduction in the Ant and Ret limb of A V nodal reentry circuit as compared to Group I The ability to induce tachycardia with relatively small increases in A H intervals on the other hand suggests that the A H delays may have no direct bearing on the initiation of PSVT and the site of reentry may be above the A V node *perhaps in the low atria* Intra atrial reentry in the region of the sinus node is a fairly well documented phenomenon in man[21] and conceivably such a process can also occur in other parts of the atria[22] If the sequence of atrial activation during an intra atrial reentrant tachycardia is from low to-high the distinction between A V nodal reentry and intra atrial reentry may be difficult to make The ability to initiate Group III PSVT at minimal A_2H_2 delays and the lack of correlation between Ret conduction and patterns of conduction during PSVT in these patients makes *intra atrial reentry* a distinct possibility Reentry in the low atria cannot be entirely excluded for Group I cases *However the facts* that (1) reentry was related to critical A H delays rather than atrial coupling intervals and (2) in five out of 13 patients in Group I when A blocked

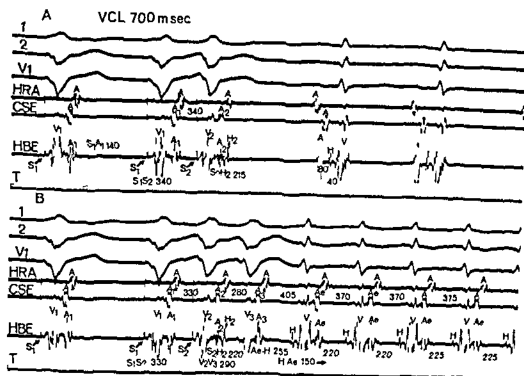


Fig 12 Retrograde refractory period pattern (Group II patient No 15) At a basic ventricular cycle length of 700 msec and an S_1S_2 of 340 msec *(Panel A)* A_2 response occurs via an accessory pathway S also conducts to the bundle of His with an S_2H_2 of 215 msec Note the absence of ventricular pre-excitation during sinus beat At shorter S S, and longer S H, delay *(panel B)* V_2 is followed by another ventricular beat (V) from reentry within the HPS V_3 in turn activates the atria (A_3) via the anomalous pathway and at the same time blocks below the bundle of His A finds the normal pathway recovered sufficiently and antegradely conducts to start the tachycardia

valid if the induced beat precedes the Ant H by an interval less than the H V intervals of sinus beats since the V H *interval (during right* ventricular apical pacing) almost always exceeds the *H V interval*[13] *However*, if the premature ventricular beat precedes the Ant H by more than the H V interval of sinus beats then it is theoretically possible to engage the Ret limb of an A V nodal reentry circuit which will make it *difficult to determine whether the reentry* is occurring within the A V node or via an AP It was however noted in this study that single ventricular premature beats rarely had any effect in Group I and III patients whereas the PSVT was *uniformly terminated in* Group II patients The lack of effect of single premature ventricular beats may be due to either (a) that the reentry circuits in Groups I and III were located farther away from the site of stimulation (i e the A V node or atrium) and/or (b) the premature ventricular beats blocked retrogradely below the *bundle of His which will obviously have no effect* upon the reentry in or above the A V node but could still engage a Kent bundle

3 Antegrade and retrograde conduction ratios during PSVT A relatively simple and reproducible finding which suggested the site of reentry was the H Ae and Ae H relationship Neither the H Ae intervals nor the H Ae Ae H showed any overlap of values between the three groups in this *series of patients*

In Group I in whom the site of reentry was the A V node, the Ae had a constant relationship with the H over a wide range of PSVT rates and the Ae never preceded the H or followed the end of ventricular electrogram in HBE recording If functional and/or anatomic duality of A V nodal pathways is the *basis of reentry in these patients* then it is conceivable that Ant block in one pathway with prolonged conduction (A H interval) in the other pathway may allow good conduction in the Ret limb of reentry circuit and account *for the short* H Ae intervals The short H Ae in turn will be followed by longer Ae H *interval and if such a conduction is stabilized the* pattern of Group I PSVT will emerge Theoretically conduction in Ant and Ret limbs of A V nodal reentry circuit could balance such that the H Ae and Ae H intervals *may approximate each other (pattern* of Group II) or the H Ae may exceed the Ae H interval (pattern of Group III) *This however did not occur in any of the* patients in Group I at any time

The presence of relatively *longer H Ae inter*vals during PSVT in Group II patients was not surprising since the *H Ae intervals included*

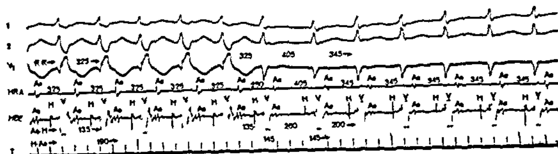


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conduction times (1) in the HPS (the H V interval) (2) from the onset of ventricular activation to the Ret penetration of the AP (3) within the AP and (4) to the atrium in the vicinity of HBE recording site It is to be noted that since most anomalous connection of the Kent bundle type are located around the base of the heart (i e A V ring) a significant amount of time may elapse between the ventricle activation via the normal pathway and Ret penetration of the AP This is probably true for both patients with or without evidence of Ant ventricular pre excitation (the delta wave) One can argue that if an atrial recording was made in closer proximity to the atrial end of the AP the H Ae (where the Ae is recorded from an atrial site close to the AP) will be shorter Although this is true the Ae as recorded on the HBE usually occurs late enough to be clearly separated from the ventricular electrogram regardless of the atrial and ventricular end of the bypass insertion Patients with septal connections may have shorter H Ae and V Ae intervals compared to those with more lateral connection However the H Ae and Ae H interval relationship presented here for Group II cases appears to be the rule rather than the exception in patients with WPW syndrome in whom reentry via a bypass was documented with epicardial mapping technique The ratios presented in Table II were obtained during normal intraventricular conduction and it goes without saying that abnormal intraventricular conduction during PSVT in these cases may significantly change these ratios

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proximal to the His bundle the PSVT could not be initiated even at closer A_1A_2 intervals argue against intra atrial reentrant process

Although good correlation existed between the site of reentry and H Ae and Ae H ratios in the present series of patients a clear cut distinction may not be always possible However, the presence of such a relationship in any patient should alert one to the possible sites of reentry which can then be confirmed or excluded with various electrophysiologic interventions mentioned above

Role of A V nodal bypass tracts in PSVT Although Ret conduction during PSVT and ventricular pacing in Group I patients occurred via the same pathway it is not certain whether the Ret conduction occurred via the A V node or a partial A V nodal bypass tract [23] In a similar manner the pattern of PSVT seen in Group III may represent Ant conduction via a partial A V nodal bypass tract and Ret conduction through the A V node The presence or absence of such partial A V nodal bypass tracts and their role in PSVT is not certain at this writing

From the results of this study one can reasonably exclude the utilization of complete A V nodal bypass tracts for Ret conduction since in all Group I patients the Ret H A intervals corrected from the rate of PSVT exceeded the H Ae intervals The two intervals will be expected to be the same if the AP completely bypassed the A V node and directly inserted into the bundle of His Since the H A intervals were only slightly longer than H Ae intervals (by $\geq$ 20 msec on the average) it appears that the point of turn around (crossover fibers) was probably located in the distal portion of the A V node (i e, the N H region)

Significance of better V A conduction in patients with PSVT The majority of patients in Groups I and II had better V A than A V conduction 10 out of 17 patients) i e 1 1 V A response was maintained at faster paced rates compared to the A V response [13] In six out of 17 patients a 1 1 response occurred in both directions up to maximum comparable paced rates and in only one out of 17 patients was the A V conduction better than V A conduction In Group III the A V conduction was either better than V A conduction (one out of 13 patients) or conduction in both directions was equal

The existence of good V A conduction in Group II patients is not surprising and is comparable to patients with Wolff Parkinson White syndrome [17] If it is assumed that Group I patients utilize A V node for a Ret conduction then the presence of better V A conduction in this group is a unique and interesting finding since the majority of the patients without PSVT have better A V conduction [13] If Ret conduction in Group I did indeed occur across the A V node it is obvious that these patients had remarkably good and rapid Ret A V nodal conduction (i e H A interval) These observations suggest that the presence of relatively good Ret conduction displayed by Group I cases might make them prone to PSVT

In the majority of Group I patients the AVCS maintained a 1 1 A V response at faster rates during PSVT compared to the paced atrial rates This indicates that either the reentrant impulse short circuited a portion of the A V node (in which case the atrium was not an essential link in the reentry circuit), or the Ae penetrated the A V node from a different site compared to the paced atrial impulse bypassing the more refractory areas of the A V node Such a difference in A V nodal response from different sites of pacing has been previously demonstrated [24] Perhaps one or both mechanisms mentioned above are operative in different patients

No such conclusions as drawn above for Groups I and II could be drawn for Group III since no consistent relationship existed between the pattern of PSVT and Ret conduction

An extremely important observation was the presence of intact V A conduction in all patients in this series The absence of V A conduction (Ret A V nodal block) is a relatively common finding in patients without PSVT [13] It is doubtful if a reentrant process (both via A V node and AP) can ever occur in the absence of V A conduction The existence of atrial tachycardia in patients without V A conduction should alert one to the possibility of intra atrial reentry or ectopic atrial automaticity

Role of A H delays in initiating PSVT Although PSVT was initiated at certain A H delays in all patients their role was different in the three groups In Group I the A V nodal conduction was essential for the reentrant process to manifest itself In Group II the degree of A H delay was relevant to the extent it produced A V prolongation For Group III cases the PSVT could be induced at shortest A H intervals and as pointed out above the role of such delays in

initiating the reentrant process is not certain If it is possible to induce atrial automaticity with atrial stimulation then this additional possibility must also be considered as a possible mechanism of tachycardia in Group III patients [23]

Patterns of refractory periods The Ant refractory period studies per se were not of much help in determining the site of reentry in the three groups However the Ret refractory period studies as well as the comparison between the Ant and Ret refractory periods provided a great deal of new information as follows

In Group I patients A V node determined the FRP of the AVCS in all patients In the same group HPS determined the FRP of the VACS in 12 out of 13 patients Since the Ant refractoriness (of the A V node) exceeded the Ret refractoriness (of the HPS) the FRP of the AVCS significantly exceeded the FRP of the VACS This is in direct contrast to the findings in other subjects without PSVT in whom the FRP of the VACS generally exceeds that of the AVCS [3] The above findings also explain why the PSVT in Group I generally terminated in the Ant limb i e Ae blocked in the A V node

The pathway utilized for Ret conduction in Group I patients in addition to good conduction also had shorter refractoriness than that of the HPS These findings have important electrophysiologic implications It is generally accepted that A V nodal reentry represents functional duality of the pathways having different refractory period and conduction velocities When Ant block is induced in the fast conducting pathway (with longer refractoriness) conduction occurs exclusively via the slow pathway (with shorter refractoriness) [24] If the conduction delay along the slow pathway is sufficient the impulse can cross over and engage the fast pathway for Ret propagation to initiate a PSVT The so called fast pathway " however did not demonstrate any evidence of longer refractoriness during Ret conduction or refractory period studies In addition the slow pathway was never used exclusively for Ret conduction and hence appeared to have longer refractoriness than the fast pathway The significance of these findings and their relationship to Ant conduction patterns remains uncertain at this writing

The Ret refractory period pattern in Group II was quite similar to patients with Wolff Parkinson White syndrome A point of caution is that unless the Ret ERP of the bypass is less than the A V node and the HPS one may not be able to demonstrate presence of a bypass during ventricular premature stimulation even though the bypass tract is used during PSVT

The longer refractoriness of the AVCS relative to the VACS explains the termination of PSVT in the Ant limb in all the Group II cases

In Group III the FRP of the VACS exceeded that of the AVCS The PSVT in these patients uniformly terminated in the Ret limb which suggest that the refractoriness of the Ret limb was longer than the Ant limb if the process was A V nodal reentry On the other hand if intra atrial reentry or ectopic atrial automaticity were the mechanisms of PSVT in these pateints it is easy to explain why the Ae did not follow an H when the intra atrial reentrant or ectopic process was terminated

Summary

In 20 patients with PSVT without ventricular pre excitation the site of reentry and functional characteristics of Ant and Ret pathways were studied Three distinct patterns of PSVT were observed In 13 patients (group I) in whom A V node was the site of reentry the interval between the Ant H bundle deflection and the following atrial echo response (H Ae) measured 30 to 85 msec and the Ae was partially or completely obscured by ventricular electrogram The ratio between the H Ae and the subsequent Ae H interval ranged 1 3 1 17 3 In a majority of Group I patients (eight out of 13) the Ret conduction was better than Ant conduction as the VACS sustained a 1 1 response at faster paced rates than AVCS The FRP of the AVCS in Group I was determined by the A V node in all patients and significantly exceeded the FRP of the VACS the latter was determined by the HPS in 12 out of 13 patients In four patients (Group II) a V A AP silent antegradely was operative during PSVT The H Ae in Group II valued 145 to 200 msec and the Ae clearly followed the ventricular electrogram the H Ae Ae H being 1 0 5 1 7 The V A conduction in all Group II patients was better than the A V conduction A V node determined the FRP of the AVCS whereas AP determined the FRP of the VACS in Group II patients and the former significantly exceeded the latter Good correlation existed between PSVT Ant and Ret conduction patterns in Group I and Group II patients

In three patients (Group III) the H Ae

measured 270 to 470 msec with an H Ae Ae H of 1 0 2 0 4 a relationship quite the opposite of Group I patients No definite relationship existed between PSVT Ant and Ret conduction patterns in Group III patients The data in Group III patients were compatible with (1) A V nodal reentry with reversal of conduction balance compared to Group I, (2) intra atrial reentry, and (3) enhanced atrail automaticity

It is concluded (1) the site of reentry in patients with PSVT is variable (2) a fair estimation of reentry site can be made from H Ae and Ae H relationship (3) all patients with PSVT have intact V A conduction and in most the V A conduction is better than A V conduction, and (4) in the majority of patients with PSVT refractoriness of the AVCS exceeds that of the VACS

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Experimental and laboratory reports

A possible role of noradrenaline in the development of myocardial infarction

An experimental study in the isolated rat heart

Anders P Waldenstrom
Ake C Hjalmarson
Lars Thornell
Göteborg and Umeå Sweden

The concept that acute myocardial infarction is caused by coronary artery thrombosis or occlusion has been the subject of considerable debate during recent years Some studies on autopsy material imply that the coronary thrombosis is the cause of myocardial infarction while other studies show that the coronary artery thrombosis is a secondary phenomenon The same conclusion is drawn by Erhardt and co workers who have studied the incorporation of I labelled fibrinogen into the coronary thrombosis of patients suffering from myocardial infarction

Ischemia may be defined as an imbalance between the metabolic demand of a tissue and its supply of oxygen fluid and substrates It is well known that elevation of sympathetic activity will cause increase in the myocardial energy demand Ischemia may develop which has been shown to result in local release of noradrenaline The present investigation uses an *in vitro* perfusion technique to study the deleterious effects of circulating and endogenous noradrenaline as demonstrated by the leakage of creatine phosphokinase (CK) from the myocardium depressed tissue concentrations of creatine phosphate and ATP and ultrastructural changes The effects of pretreatment with a beta blocker (*metoprolol*) a calcium antagonist (verapamil) or a membrane stabilizer (lidocaine) in preventing the detrimental effects of noradrenaline have also been studied It is suggested that the release of myocardial noradrenaline may play an important role in the myocardial infarction process

Material and methods

Perfusion procedure Male Wistar rats weighing 350 to 450 Gm and fed a standard pellet diet and water *ad libitum* were heparinized (2 5 mg intraperitoneally) 30 minutes prior to pentobarbital anesthesia (60 mg /kg of body weight intraperitoneally) The hearts were quickly excised and immersed in ice chilled *isotonic saline As soon as the* heart had stopped beating it was mounted in the perfusion apparatus by cannulating the aorta and left atrium The working rat heart perfusion technique described by Neely and co-workers had been modified by Waldenstrom and Hjalmarson to permit retrograde perfusion of the hearts with constant perfusion pressure and recirculating buffer The hearts were perfused with 90 ml of recirculating Krebs Henseleit bicarbonate buffer (pH 7 4) with glucose (14 mM) and ascorbic acid (0 1 mg /ml) added The buffer was continuously gassed with 95 per cent O_2 and 5 per cent CO_2 equilibrated with H_2O at 37° C The atrial filling pressure was 10 cm H_2O and the hearts worked against a hydrostatic pressure of 80 cm H_2O

All hearts were initially perfused according to

measured 270 to 470 msec with an H Ae Ae H of 1 02 0 4, a relationship quite the opposite of Group I patients No definite relationship existed between PSVT Ant and Ret conduction patterns in Group III patients The data in Group III patients were compatible with (1) A V nodal reentry with reversal of conduction balance compared to Group I, (2) intra atrial reentry, and (3) enhanced atrial automaticity

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followed by perfusion with buffer containing glutaraldehyde (2.5 per cent) for 15 minutes at +4° C. The hearts were then fixed in the glutaraldehyde solution for an additional 6 hours. After fixation the hearts were rinsed in Tyrode's solution while slices of about 1 mm were cut from the midregion of the ventricles. From these slices the free left ventricular wall was subdivided into five groups of tissue blocks of 1 mm^3 so that each group of blocks represented successive layers of the myocardium from the endocardium to the epicardium. The blocks were postfixed in 1 per cent osmium tetroxide in Tyrode's solution for 2 hours, rinsed in buffer, dehydrated in graded series of acetone and finally embedded in Vestopal W. Ultrathin slices were cut in a LKB Ultratome* and the slices were collected on formvar coated keyhole or meshgrid stained with uranil acetate and lead citrate before examination in a Philips EM 300 Electron Microscope.

Statistics

Comparisons between means were performed with the Student's t test. A p value ≤ 0.05 was considered significant in this study.

Results

Effects of endogenous noradrenaline

Coronary and aortic flows. There was no change in coronary flow caused by the addition of noradrenaline to the perfusion medium in concentrations of 10 M to 10 M (Table I). On the other hand, there was a decrease in aortic flow at concentrations of 10 M or greater.

Myocardial content of ATP and creatine phosphate. Hearts perfused for 45 minutes with noradrenaline had lower contents of ATP but an accumulation of creatine phosphate with increasing noradrenaline concentrations in the buffer (Fig. 1).

Release of ASAT and CK to the perfusion medium. There was a leakage of ASAT and CK from well perfused hearts when noradrenaline was added to the perfusion buffer (Fig. 2). A dose-response relationship between the concentration of noradrenaline and the leakage of enzymes was demonstrated. A concentration of 10 M of noradrenaline did not cause a greater leakage of ASAT or CK than in controls. At a concentration

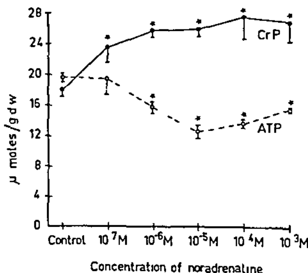


Fig. 1. Effects of different concentrations of noradrenaline on myocardial ATP and creatine phosphate (*CrP*). The hearts were perfused anterogradely for 15 minutes and retrogradely for 30 minutes. Each value represents the *mean* ± *SE for 6 to 8* hearts. * = significantly different from the control ($p < 0.05$).

of 10 M of noradrenaline, however, there was a significant leakage of both enzymes which was further increased by 10 M of noradrenaline. Addition of 10 M, however, did not cause any further increase in leakage. The increases in the activities of ASAT and CK became statistically significant after 25 minutes of perfusion when perfused with noradrenaline 10 M to 10 M.

Changes in myocardial ultrastructure. Ultrastructural lesions were seen in the myocardium of hearts perfused with noradrenaline. Damaged muscle fibers were scattered throughout the myocardium without any preferential location. At low concentrations of noradrenaline (10 M) the myocardial lesions consisted mainly of single affected myocardial fibers surrounded by perfectly normal cells. At higher concentrations of noradrenaline the number of damaged cells was increased and clusters of affected cells were seen. The capillaries always appeared to be open and had a normal ultrastructure (Fig. 3). The morphology of the affected cells was highly variable, however, with regard to the characteristics of the lesions. Three main types of affected cells were observed (Figs. 3 to 5). The most common lesion was cells with myofibrils showing various degrees of hypercontraction independent of the noradrenaline concentration in the perfusion solution. The mitochondria were rounded and

*LKB Bromma, Sweden.

Table I Aortic and coronary flow for hearts perfused with different concentrations of noradrenaline (NA) in the perfusion buffer

		Aortic flow					Coronary flow				
Group	Time (min)	0	5	10	15	45 + 2	0	5	10	15	45 + 2
Control		35 ± 2*	34 ± 2	35 ± 1	34 ± 2	35 ± 2	19 ± 1	19 ± 1	20 ± 1	20 ± 1	16 ± 2
NA 10 M		35 ± 1	38 ± 2	38 ± 1	36 ± 2	34 ± 3	20 ± 1	20 ± 0	20 ± 1	20 ± 1	23 ± 2
NA 10 M		37 ± 2	35 ± 1	36 ± 1	36 ± 2	29 ± 2†	20 ± 0	20 ± 0	21 ± 1	21 ± 0	20 ± 0
NA 10 M		37 ± 3	31 ± 3	33 ± 2	33 ± 2	25 ± 1†	20 ± 1	19 ± 1	18 ± 1	19 ± 1	20 ± 1
NA 10 M		31 ± 1	27 ± 2	28 ± 1	27 ± 1†	18 ± 2†	20 ± 2	20 ± 1	19 ± 1	19 ± 1	19 ± 1

The values are estimated just before addition of noradrenaline and 5 10 and 15 minutes later The hearts were then perfused for 30 minutes in the retrograde way and thereafter for 2 minutes as working preparations before the final estimation (45 + 2) Each value represents the mean ± SE for 6 to 8 hearts.
† = significantly different from the initial value ($p \leq 0.05$)

Langendorff for 10 minutes and as a working preparation for 2 minutes to allow for stabilization and washout of blood Thereafter the drugs were added and the hearts subjected to different concentrations of noradrenaline and metoprolol verapamil or lidocaine were perfused anterogradely for 15 minutes and retrogradely for 30 minutes Hearts exposed to tyramine were perfused anterogradely for 60 minutes The hearts taken for histological examination were perfused anterogradely and retrogradely for 60 minutes respectively

Noradrenaline bitartrate was dissolved in Krebs Henseleit buffer with ascorbic acid added One ml of the noradrenaline solution was added to the recirculating buffer to give a final concentration of 10 M 10 M Tyramine HCl was dissolved in the perfusate and added to the recirculating buffer to give a final concentration of 250 µg/ml Metoprolol* was dissolved in perfusate to give a final concentration of 10 M in the buffer used for perfusion of the tyramine treated hearts and 10 M for the perfusion of noradrenaline treated hearts Standard solutions of lidocaine† and verapamil‡ were used to give final concentrations of 10 M and 10 M respectively Metoprolol verapamil or lidocaine were added 60 seconds before addition of noradrenaline

Chemical analyses For one group of hearts the perfusion was terminated by clamping the still beating heart with a Wollenberger clamp precooled in liquid nitrogen The hearts were powdered in a percussion mortar at the temperature of liquid nitrogen A sample of this powder was taken for biochemical analysis Myocardial glycogen was split by amylase and determined according to a glucose oxidase method described by Saifer and Gerstenfeld[11] with rabbit liver glycogen used as a standard Tissue lactic acid was estimated by the enzymatic method of Lundholm and co workers[12] ATP and creatine phosphate contents were assayed by an enzymatic method described by Lamprecht and Trautschold[13]

Samples from the perfusion fluid were taken at regular intervals for biochemical analysis The release of aspartate aminotransferase (ASAT EC 2 6 1 1) and creatine phosphokinase (CK, EC 2 7 3 2) from the myocardium to the perfusate was estimated by measuring the activities of these enzymes at 35° C in buffer samples using a LKB 8600 Reaction Rate Analyzer* and standard UV test kits† The cardiac output and coronary flow were measured by collecting the perfusate in a graduated cylinder and calculating the volume per unit time

Histological examinations The hearts used for histological examination were arrested in diastole by perfusion with buffer at +4° C immediately

*Metoprolol (Seloken) A B Hassle Göteborg, Sweden.
†Lidocaine (Xylocard) A B Hassle Göteborg, Sweden
‡Verapamil (Isoptin) Knoll A G Ludwigshafen am Rhein West Germany

*LKB Bromma Sweden
†Biochemical Test Combination Boehringer Mannheim GmbH West Germany

followed by perfusion with buffer containing glutaraldehyde (2 5 per cent) for 15 minutes at +4 C The hearts were then fixed in the gluta raldehyde solution for an additional 6 hours After fixation the hearts were rinsed in Tyrode s solution while slices of about 1 mm were cut from the midregion of the ventricles From these slices the free left ventricular wall was subdivided into five groups of tissue blocks of 1 mm³ so that each group of blocks represented successive layers of the myocardium from the endocardium to the epicardium The blocks were postfixed in 1 per cent osmium tetroxide in Tyrode s solution for 2 hours rinsed in buffer dehydrated in graded series of acetone and finally embedded in Vestopal W Ultrathin slices were cut in a LKB Ultratome and the slices were collected on formvar coated keyhole or meshgrid stained with uranil acetate and lead citrate before exam ination in a Philips EM 300 Electron Micro scope

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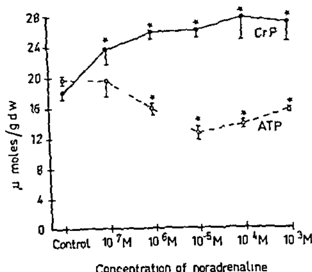


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of 10 M of noradrenaline however there was a significant leakage of both enzymes which was further increased by 10 ⁵M of noradrenaline Addition of 10 M however did not cause any further increase in leakage The increases in the activities of ASAT and CK became statistically significant after 25 minutes of perfusion when perfused with noradrenaline 10 ⁶M to 10 M

Changes in myocardial ultrastructure Ultra structural lesions were seen in the myocardium of hearts perfused with noradrenaline Damaged muscle fibers were scattered throughout the myocardium without any preferential location At low concentrations of noradrenaline (10 ⁷M) the myocardial lesions consisted mainly of single affected myocardial fibers surrounded by perfect ly normal cells At higher concentrations of nor adrenaline the number of damaged cells was increased and clusters of affected cells were seen The capillaries always appeared to be open and had a normal ultrastructure (Fig 3) The morphology of the affected cells was highly vari able however with regard to the characteristics of the lesions Three main types of affected cells were observed (Figs 3 to 5) The most common lesion was cells with myofibrils showing various degrees of hypercontraction independent of the noradrenaline concentration in the perfusion solution The mitochondria were rounded and

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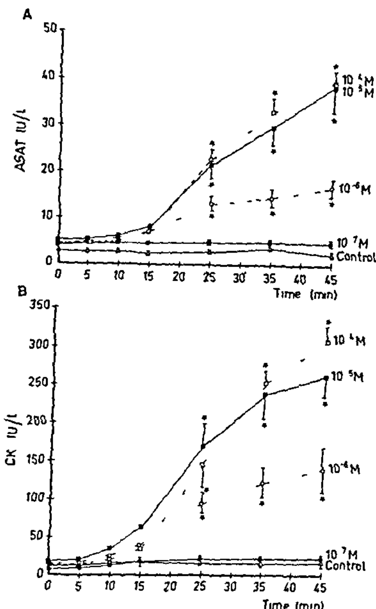


Fig 2 A (upper panel) Release of ASAT from the hearts to the perfusion medium when perfused with different concentrations of noradrenaline After 15 minutes of antero grade perfusion 30 minutes of retrograde perfusion followed *B (lower panel)* Release of CK under the same conditions as in panel *A* Each value represents the mean ±SE for 6 to 8 hearts * = significantly different from the initial value ($p < 0.05$)



Fig 3 Low power electron micrograph of cross sectioned myocardium from a rat heart perfused with noradrenaline 10⁻⁵ M Normal cells *(left part of panel)* have a typical pattern of mitochondria and myofibrils In the affected cells *(right part of panel)* this regular pattern is lost A few cells have a high electron opacity *(arrows)* The distribution of patent capillaries is uniform (Original magnification ×660)

enlarged with an electron translucent matrix often containing flocculent densities and para crystalline material (Figs 4 and 5) Some of the cells with this type of damage showed signs of disintegration in connection with sarcolemmal ruptures

The affected myocardial cells of the second type of lesion also contained abnormal myofibrils The sarcomeric bands were indistinct and espe cially the A bands were of low density The mitochondria on the other hand were very elec tron-dense with inner membranes either in twisted zigzag or tubular configuration (Fig 6)

The third type of myocardial cell damage was characterized by cells of a high over all electron opacity In low magnification in cross sections the normal checkerboard pattern due to myofib rils and mitochondria appeared to be lost (Fig 3) *At higher magnification myofibrils with a normal* banding pattern could be distinguished inter spersed with mitochondria as in normal myocar dial fibers

Protective effects of metoprolol verapamil and lidocaine on hearts perfused with noradren aline As shown in Fig 2A there was a significant release of ASAT when hearts were perfused with noradrenaline compared to controls This leakage was significantly reduced by pretreatment with metoprolol verapamil, or lidocaine There were no significant differences in the release of ASAT between the three groups at the chosen concentrations (Fig 7) The noradrenaline depen dent decrease in myocardial ATP content was prevented by metoprolol verapamil or lidocaine The noradrenaline induced increase of creatine phosphate however did not seem to be prevented by metoprolol verapamil or lidocaine (Table II)

Effects of tyramine on myocardial contents of ATP creatine phosphate and leakage of CK Tyramine caused no significant reduction in myocardial ATP content (Table III) The increase in creatine phosphate was however not influenced by pretreatment with metoprolol



Fig 4 Longitudinally sectioned myocardial fibers The three central fibers contain myofibrils in various stages of hypercontraction Some extensive contraction bands are *indicated by arrows* The mitochondria in these cells are translucent enlarged and often containing matrix densities The neighbouring cells ( ) contain electron dense mitochondria *(m)* The myofibrils in these cells have an ill defined banding pattern as described for the second type of lesion in the hearts perfused with noradrenaline A normal muscle fiber is seen in the *upper right corner* c = capillary (Original magnification ×3000)



Fig 5 Cross-section of two muscle fibers The fiber to the *right appears relatively* normal while the other one shows swollen mitochondria *(m)* with a translucent matrix Matrix densities are evident *at arrows* c = capillary (Original magnification ×19000)

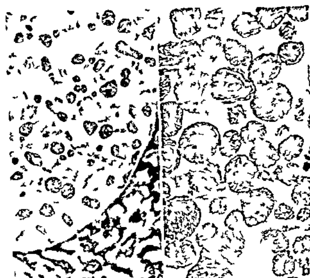


Fig 6 *a* Cross-section of a myocardial fiber with intracellular edema Myofibrils appear to be in a stage of lysis *(arrows)* The mitochondria are dense with inner membranes in a tubular configuration The adjacent cell is normal in appearence (Original magnification ×3000) *b* Higher magnification of mitochondria with inner membranes in a tubular or zigzag configuration (Original magnification ×19000)

Tyramine perfusion also resulted in a leakage of CK which was significantly reduced during perfusion with tyramine in combination with metoprolol (Fig 8)

Discussion

The cardiotoxic effects of adrenaline were discovered by Josué already in 1907 Other catecholamines have also been shown to have cardiotoxic effects when given in large doses to animals[1] High levels of circulating catecholamines in patients with pheochromocytoma are believed to be responsible for the cardiomyopathy seen in this disease Different mechanisms for the cardiotoxic effect of catecholamines have been suggested including an imbalance between myocardial oxygen demand and supply platelet aggregation resulting in coronary thrombus formation[1] and disturbances in microcirculation

Hearts perfused with noradrenaline were damaged as demonstrated by decreased cardiac output leakage of myocardial enzymes and ultrastructural alterations Since an isolated heart preparation perfused with a medium free of

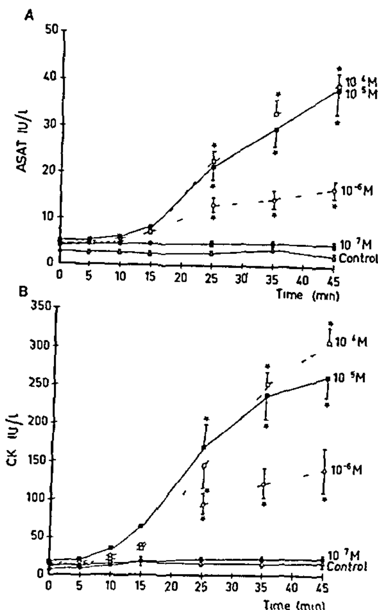


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enlarged with an electron translucent matrix often containing flocculent densities and para crystalline material (Figs 4 and 5) Some of the cells with this type of damage showed signs of disintegration in connection with sarcolemmal ruptures

The affected myocardial cells of the second type of lesion also contained abnormal myofibrils The sarcomeric bands were indistinct and especially the A bands were of low density The mitochondria on the other hand were very electron-dense with inner membranes either in twisted zigzag or tubular configuration (Fig 6)



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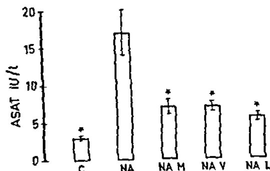


Fig 7 Release of ASAT from hearts perfused anterogradely for 15 minutes and retrogradely for 30 minutes with noradrenaline 10 M (*NA*) and metoprolol 10 M (*M*) verapamil 10 M (*V*) or lidocaine 10 M (*L*) Each bar represents the mean ±SE for 6 to 8 hearts = significantly different from NA ($p < 0.05$)

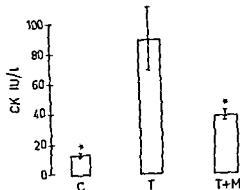


Fig 8 Release of CK from hearts perfused anterogradely for 60 minutes with tyramine 250 µg/ml (*T*) with or without metoprolol 10 M (*M*) Controls are perfused without addition of tyramine or metoprolol Each bar represents the mean ±SE for 6 to 8 hearts = significantly different from tyramine treated hearts ($p < 0.05$)

tion A membrane stabilizing effect of this drug has also been proposed Local application of lidocaine on experimental ischemic dog hearts has been shown to decrease noradrenaline release though the mechanism of this effect is not fully understood [3]

Ultrastructural examination of the hearts also revealed the dose dependent damage caused by noradrenaline However it was evident that different types of lesions of myocardial cells were inflicted by noradrenaline perfusion At least three types of myocardial fiber lesions were observed The most frequent type of lesion—myocardial fibers with hypercontracted myofibrils and swollen mitochondria—has previously been recognized by many investigators as characteristic of many cardiomyopathies especially those related to catecholamine induced necrosis [3] This type of lesion was referred to as coagulative myocytolysis by Baroldi [ ] who observed it in 68 per cent of patients with sudden coronary deaths

The second type of lesion in this study consisted of myocardial cells with myofibrils in a stage of lysis and mitochondria that *in situ* according to the terminology of Korman and coworkers,[**] can be referred to as having an energized twisted or zigzag configuration Whether the structure of such mitochondria does reflect different metabolic states or not has been debated extensively The proposal that the intramitochondrial reorganization represents a mechanism for energy conservation has been discarded It seems more likely that such changes are involved in metabolic control [9] Undoubtedly the metabolic situation in this type of lesion is different from that in the previous type This second type of lesion might correspond to the lesion which Baroldi[15] called colliquative myocytolysis and which is supposed to be typical of cells dying in a failing state

The third type of lesion seen here might be the same as that of certain cells seen in human myocardial lesions in which the structure of the entire cell is indistinct [3]

It can be concluded that the diversity of reactions in the myocardial cells appears to be independent of the relationship between cells and capillaries since the lesions are diffusely scattered over the myocardium and the capillaries were uniformly patent

The biochemical analyses of whole hearts do of course reflect the combined effects of all the cells Since the far most common lesion was of the first type i e the type found in cardiomyopathy enzyme release is probably related to this type of lesion The unpredictable rise of creatine phosphate might on the other hand be related to other types of lesions The ultrastructure of noradrenaline perfused hearts was similar to that seen in ischemia[4] and may be related to the different types of lesions described by Baroldi [3] Thus catecholamines may induce myocardial cell damage of the same type as seen in acute myocardial infarction

The initial event leading to acute myocardial infarction has recently been debated [1] The present study has shown the detrimental effects

Table II Effects on myocardial ATP and creatine phosphate for hearts perfused with noradrenaline 10 ⁻⁶M and in presence of metoprolol 10 ⁻⁶M verapamil 10 ⁻⁶M or lidocaine, 10 ⁻⁶M

	Control	*NA*‡	*NA + M*	*NA + V*	*NA + L*
ATP (µmol/Gm dry weight)	19 7 ± 0 6	15 9 ± 0 6†	21 3 ± 2 3	20 5 ± 0 8	21 9 ± 1 4
Creatine phosphate (µmol/Gm dry weight)	18 3 ± 1 0	25 8 ± 1 3†	28 3 ± 2 1†	30 6 ± 1 6†	28 6 ± 1 [illegible]

The hearts were perfused for 15 minutes as working preparations and retrogradely for 30 minutes Each value represents the mean ± SE for 6 to 8 hearts
† = significantly different from controls (p ≤ 0 05)
‡Abbreviations NA = noradrenaline M = metoprolol V = verapamil L = lidocaine

Table III Effects on myocardial ATP and creatine phosphate for hearts perfused with tyramine 250 µg/ml, with or without metoprolol 10 ⁻⁶M

	Control	*Tyramine*	*Tyramine + metoprolol*
ATP (µmol/Gm dry weight)	16 1 ± 0 5*	15 3 ± 0 6	17 3 ± 1 0
Creatine phosphate (µmol/Gm dry weight)	22 3 ± 1 4	24 5 ± 0 6	26 0 ± 1 7

The hearts were perfused for 60 minutes as working preparations Each value represents the mean ± SE for 5 to 6 hearts

blood was used the demonstrated effects of noradrenaline could not have been due to effects of the sympathetic nervous system lipolysis of adipose tissue or reduction of coronary flow due to platelet aggregation The dose dependent effects of noradrenaline on the leakage of ASAT and CK speak in favor of the theory of increased metabolic demand as the cause of the myocardial damage seen in this study

The normal plasma adrenaline level under physiological conditions is in the order of 10 ⁻⁹M to 10 M The noradrenaline concentration of rat myocardium is about 600 ng /Gm The concentration of noradrenaline in a homogenate of heart can thus be expected to be about 10 ⁻⁶M The higher concentrations of noradrenaline used in this study were unphysiological but local concentrations of noradrenaline within the heart can be in the order of 10 M or even higher if the myocardial stores of noradrenaline are rapidly depleted during anoxia or ischemia as shown by Wollenberger and associates

The sympathomimetic action of tyramine is exclusively due to the depletion of catecholamine stores When tyramine was added to the perfusion buffer there was a marked release of CK which was prevented by concomitant perfusion with the beta blocker metoprolol This indicated that the amount of noradrenaline stored in the heart is enough to induce cellular damage Since leakage of CK and decrease of ATP are prevented by metoprolol it seems that the adverse effects of tyramine are mediated via beta receptors and are not unspecific toxic effects

Noradrenaline did not alter coronary flow but with noradrenaline concentrations of 10 ⁻⁶M or more there was a reduction of cardiac output as a sign of cardiac failure and leakage of CK indicating cell damage As already shown by others myocardial glycogen was depressed and lactate accumulated in catecholamine perfused hearts The decrease of ATP content has been described earlier but the concomitant increase of creatine phosphate content found here needs further explanation When isoproterenol was given to rats a decrease of myocardial ATP was demonstrated while creatine phosphate levels were still unchanged One explanation might be a decreased activity of the pH sensitive CK due to lactate accumulation The release of CK from the heart demonstrated in this study will further reduce the intracellular activity of this enzyme

The effects on the slow Ca channels of the cell membrane by catecholamines result in enhanced Ca influx which in turn may cause Ca overload and cellular injury as proposed by Fleckenstein and co workers The cardioselective beta blocker metoprolol and the membrane stabilizing agent lidocaine as well as the calcium antagonistic drug verapamil all showed protective effects against noradrenaline induced myocardial damage by their respective specific actions at different cellular levels Beneficial effects of beta blockade on the ischemic myocardium have been described earlier Similar effects on ischemic myocardium by verapamil are probably due to the Ca antagonistic effect resulting in decreased myocardial work and oxygen consump

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of exogenous noradrenaline on well perfused hearts The fact that the rapid release of myocardial stores of noradrenaline can result also in ischemic damage to well perfused hearts supports the theory of an imbalance between the myocardial metabolic demand and the supply of oxygen, fluids and substrates [17] It is also well known that short periods of anoxia and ischemia[7] cause a release of myocardial noradrenaline which may well lead to an aggravation of the primary ischemia

From this study it can be hypothesized that acute myocardial infarction may start with a temporary relative ischemia due to a sudden increase of metabolic demand and/or atherosclerotic narrowing of coronary vessel This results in a release of stored noradrenaline that starts a vicious cycle with a further increase of the ischemic damage The protective effects of beta blockade on the ischemic myocardium [9,31] as well as the possible preventive effects in patients who sustained acute myocardial infarction[41] might at least partly be explained by the proposed role of noradrenaline in myocardial infarction

Summary

Isolated rat hearts were perfused with buffer containing noradrenaline 10^{-7} to 10^{-4}M A dose dependent depletion of glycogen and ATP were seen together with a leakage of ASAT and creatine phosphokinase (CK) The damage induced by noradrenaline could be prevented by addition of a beta blocker (metoprolol), verapamil or lidocaine to the perfusion medium When the endogenous myocardial stores of noradrenaline are rapidly depleted by perfusion with tyramine a similar cell damage was demonstrated Electron micrographs from hearts subjected to noradrenaline showed three different types of cell damage that could be correlated to earlier described findings The importance of noradrenaline for the ischemic injury was demonstrated It was hypothesized that acute myocardial infarction may start because of a sudden release of endogenous noradrenaline

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Components of the hemodynamic response to elevated cerebrospinal fluid pressure

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Elevation of cerebrospinal fluid (CSF) pressure to levels usually exceeding mean systemic blood pressure is followed by what is frequently called the Cushing reflex [1] The increased vascular pressures and cardiac output occurring with the reflex have been well described [2-3] Since intracranial pressures may increase to over 100 mm Hg with severe brain injury[4] and intracranial pressures up to 160 mm Hg have been described in patients with subarachnoid hemorrhage,[5] significant elevations of intracranial pressure have clinical importance

We have previously demonstrated that increasing CSF pressure to 200 mm Hg significantly increased cardiac output heart rate stroke volume aortic pressure pulmonary artery pressure wedge pressure right atrial pressure pulmonary capillary blood volume and pulmonary diffusing capacity [6] These changes were attributed to a massive alpha and beta adrenergic stimulation Beta adrenergic blockade prevented an increase in cardiac output and heart rate but did not alter the response of increased vascular pressures to elevated CSF pressure Alpha adrenergic blockade prevented an increase in vascular pressures during elevated CSF pressure but did not prevent the increase in cardiac output Two distinct adrenergic components were thus identified but it was unclear if the components were humorally or neurogenically mediated A subsequent study provided evidence for a circulating beta adrenergic agonist during elevated CSF pressure [7] The present study was undertaken to clarify the origin of these alpha and beta adrenergic effects during elevated cerebrospinal fluid pressure

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Methods

Mongrel dogs (21 ± 3 kilograms mean ± SD) were anesthetized with pentobarbital 30 mg/kg intravenously Ventilation with periodic hyperinflation was controlled through a cuffed endotracheal tube with a Harvard constant volume ventilator end tidal CO_2 was monitored and maintained between 5.0 to 5.5 per cent and the animals were paralyzed with intravenous gallamine triethiodide 2.0 mg/kg

For clarification the various subgroups studied with elevated CSF pressure are outlined as follows

Group I An initial six dogs studied acutely after bilateral adrenalectomy and ganglionic blockade with hexamethonium

Group II Six dogs studied 17 ± 2 days after adrenalectomy

Group III Twelve dogs studied with an isolated and perfused gracilis muscle preparation and beta adrenergic blockade

Group III A Four studied with intact adrenals with the muscle preparation denervated

Group III B Four studied 18 ± 1 days after adrenalectomy with the muscle preparation denervated

Group III C Four studied 18 ± 2 days after adrenalectomy with muscle preparation innervated

Group IV Six dogs with an isolated perfused and denervated gracilis muscle preparation alpha adrenergic blockade and intact adrenals

Groups I and II were studied as previously described [6,7] Cardiac catheters were placed in the main pulmonary artery right atrium and wedge

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position through the jugular veins and in the ascending aorta just distal to the aortic valve through the carotid artery Pressures were measured at end expiration and heart rate was determined from the pressure tracing Cardiac outputs were done in duplicate by the indicator-dilution technique and expressed as milliliters per minute per kilogram of body weight and stroke volume as milliliters per beat per kilogram Central blood volume was determined from the main pulmonary artery to ascending aorta Mean pressures were used to calculate vascular resistance Systemic vascular resistance (units) = systemic artery pressure – right atrial pressure (mm Hg)/cardiac output (ml /min per kilogram) Pulmonary vascular resistance (units) = pulmonary artery pressure – wedge pressure (mm Hg)/cardiac output (ml /min per kilogram) Arterial blood pH P_{O_2} and P_{CO_2} were determined by conventional electrodes (Instrumentation Laboratory Inc)

Cerebrospinal fluid pressure was elevated as previously described using a pressure reservoir of saline (37 C) buffered with $NaHCO_3$ to pH 7 4 connected to a needle in the cisterna magna After control period values were obtained the CSF pressure was increased to 100 mm Hg and measurements were obtained after 5 and 10 minutes The CSF pressure was then increased to 200 mm Hg the determinations repeated after 5 and 10 minutes and the CSF pressure was returned to control period levels The previously mentioned determinations were repeated 10 minutes after CSF pressure was returned to control values

In Group I the animals were studied immediately after bilateral adrenalectomy and ganglionic blockade obtained with intravenous hexamethonium chloride 5 mg of base per kilogram in a concentration of 25 mg /ml infused over 5 minutes Completeness of ganglionic blockade was determined by observing mean systemic blood pressure during 30 seconds of bilateral common carotid artery occlusion Hydrocortisone sodium succinate was given 50 mg intramuscularly at onset of adrenalectomy and 100 mg intravenously during the remainder of the study Performing the elevated CSF pressure study immediately after adrenalectomy resulted in protracted experiment of 4 to 5 hours

Subsequently in Groups II and III bilateral adrenalectomy was performed through a midline incision with sterile technique meticulous dissection and hemostasis Dogs were maintained after adrenalectomy with 12 5 mg cortisone acetate and 1 mg desoxycorticosterone acetate intramuscularly each day On the day when the dogs were subsequently studied with elevated CSF pressure 14 to 19 days post adrenalectomy they received a 25 mg intravenous bolus of hydrocortisone sodium succinate and an additional 25 mg in 50 ml of saline infused during the remaining study The amount of steroid was considered to reasonably approximate the amount that would be elaborated during severe stress by an animal with intact adrenals

The isolated perfused gracilis muscle was prepared in the dog as previously described[10, 11] Briefly the gracilis muscle was completely exposed and isolated except for minimal lateral and medial tendinous connections and the gracilis artery and vein The obturator nerve was sectioned in the denervated muscle preparations Heparin 5 mg /Kg was given intravenously and a polyethylene catheter (PE 90) was inserted in the gracilis artery and connected to a constant volume flow rate pump (Holter Pump Model 911) The contralateral femoral artery was cannulated for inflow to the pump and flow rate (11 5 ± 2 8 ml per minute mean ± SD) was adjusted so gracilis perfusion pressure approximated systemic blood pressure Pressure was monitored in the tubing between the femoral artery and perfusion pump permitting the inflow pressure to the pump to be kept constant at control levels regardless of increases in femoral artery pressure by using a screw resistor After stabilization of the muscle perfusion pressure the propranolol or phenoxybenzamine were infused

The 12 dogs (Group III) with beta adrenergic blockade and the isolated perfused gracilis muscle preparation received propranolol 0 5 mg /Kg in 30 ml saline over 5 minutes prior to obtaining control values and an additional 0 25 mg /Kg in 30 ml over the remainder of the study Four were studied with intact adrenals and denervated muscle preparation (Group III A) Four were studied after adrenalectomy with denervated muscle preparation (Group III B) Four were studied after adrenalectomy with the muscle preparation innervated (Group III C) At the conclusion of the study the completeness of beta blockade was demonstrated with intravenous isoproterenol (0 01 mg in 20 ml saline over 2

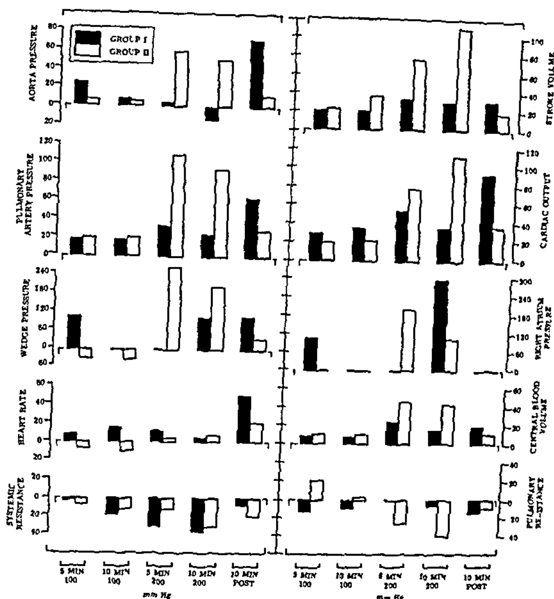


Fig 1 Per cent change from control during elevated CSF pressure Group I—adrenalectomy and ganglionic blockade Group II—adrenalectomy *Abscissa* indicates duration and magnitude of elevated CSF pressure *10 minutes post* indicates time after CSF pressure returned to control values *Asterisk* indicates change significant at P < 0 05 level

minutes) demonstrating no change in heart rate systemic blood pressure or gracilis muscle resistance

The six alpha adrenergic blockade animals (Group IV) all with intact adrenals and an isolated denervated and perfused gracilis muscle preparation received phenoxybenzamine hydrochloride (courtesy Smith Kline and French Co Philadelphia) 3 mg/kg in 25 ml saline over 60 minutes prior to obtaining values and an additional 1 mg/kg in 25 ml over the remainder of the study At the conclusion the completeness of alpha blockade was demonstrated with norepinephrine base 0 01 mg in 20 ml saline intravenously over 2 minutes demonstrating no change in heart rate systemic blood pressure or gracilis muscle resistance

The significance of the change from the control period to each of the subsequent periods was determined by Dunnett s t test at the 5 per cent level[14]

Results

The results are presented in Figs 1 and 2 In Group I animals studied acutely after adrenalectomy and ganglionic blockade control aortic pressure (92 ± 8 mm Hg mean ± SD) only changed 10 minutes after CSF pressure was returned to control values Control cardiac output (123 ± 15 ml/min per kilogram) increased significantly (P < 0 05) at 5 minutes of 200 mm Hg CSF pressure and 10 minutes after CSF pressure returned to control levels Control systemic vascular resistance (0 759 ± 0 097 units/

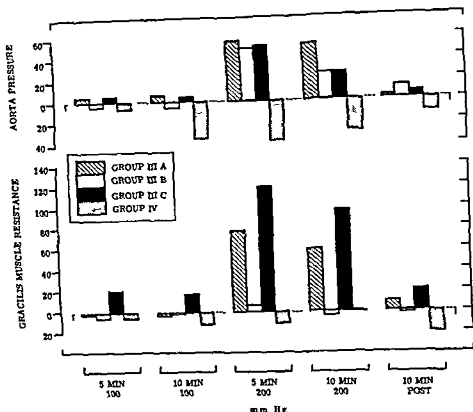


Fig 2 Per cent change from control in gracilis muscle study Group III—beta adrenergic blockade A—intact adrenals denervated muscle B—adrenalectomy denervated muscle C—adrenalectomy innervated muscle Group IV—alpha adrenergic blockade intact adrenals denervated muscle *Abscissa* and *asterisk* same as in *Fig 1*

kilogram) decreased significantly at 10 minutes 100 mm Hg and 5 minutes and 10 minutes of 200 mm Hg CSF pressure Control right atrial (−1 ± 1 mm Hg) and wedge (1 ± 3 mm Hg) pressures showed essentially no change but control pulmonary artery pressure (13 ± 2 mm Hg) increased slightly but significantly during 5 minutes 200 mm Hg CSF pressure and 10 minutes after release of CSF pressure Control heart rate (111 ± 8 beats/minute) increased significantly 10 minutes after release of CSF pressure

There were no significant changes compared to the control period for any parameter after 5 or 10 minutes of CSF pressure 100 mm Hg in Group II In Group II control aortic pressure (126 ± 5 mm Hg) pulmonary artery pressure (11 ± 3 mm Hg) wedge pressure (3 ± 4 mm Hg) cardiac output (177 ± 41 ml /min per kilogram) stroke volume (0 99 ± 0 17 ml /beat per kilogram) and central blood volume (15 2 ± 2 2 ml /kg) increased significantly ($P < 0\ 05$) at 5 and 10 minutes of CSF pressure 200 mm Hg Group II also demonstrated a significant decrease from control systemic vascular resistance (0 758 ± 0 183 units/ Kg) at 10 minutes of 200 mm Hg and after release of CSF pressure Group II demonstrated no significant changes in pulmonary vascular resistance or heart rate while a change in right atrial pressure was significant but small

In Group II the animals were weighed daily after the adrenalectomy and the weight decreased 1 ± 1 kilogram prior to the elevated CSF pressure study Serum electrolytes were determined on the day of the CSF study and were sodium 144 ± 1 potassium 4 4 ± 0 3 and chloride 108 ± 4 mEq /L

There were no changes during CSF pressure 100 mm Hg in the beta adrenergic blockade dogs (Fig 2) with the perfused gracilis muscle preparations (Group III) In the animals with intact adrenals and denervated muscle (Group III A) the control aortic pressure (131 ± 5 mm Hg) increased significantly during 5 and 10 minutes of CSF pressure 200 mm Hg The resistance of the perfused gracilis muscle increased significantly

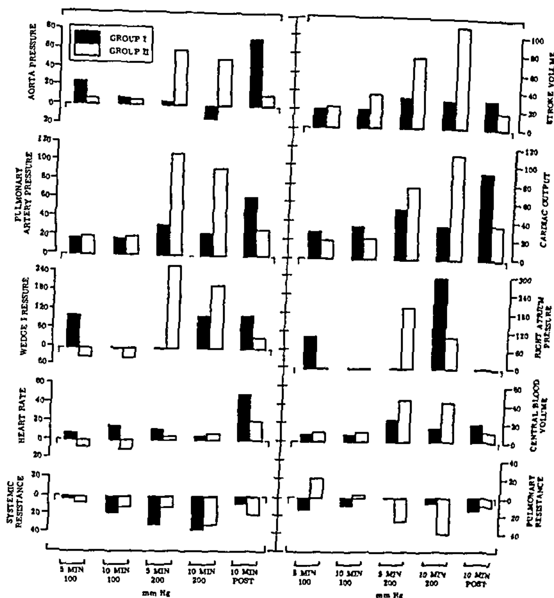


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ade There was no increase in aortic pressure during elevated CSF pressure but cardiac output increased and systemic vascular resistance decreased indicating the presence of a circulating beta adrenergic agonist independent of the adrenals The previous study also indicated a circulating beta adrenergic agonist but the adrenals were intact [9] The decrease in control blood pressure was consistent with the lowering of blood pressure found in rats and rabbits with combined chemical sympathectomy and adrenalectomy A marked increase in cardiac output and aortic pressure occurred 10 minutes after CSF pressure was returned to control levels this was noted previously in dogs with systemic hypotension during the increased CSF pressure Dogs can survive 25 minutes of cerebral ischemia[22] and a marked reactive hyperemia occurs with reperfusion of the brain [1] that may wash out vasoactive substances [2]

Group II (adrenalectomized animals) demonstrated the expected alpha and beta adrenergic effects (increase in vascular pressures cardiac output stroke volume) during CSF pressure of 200 mm Hg and therefore excluded the adrenals as the only participant in the Cushing reflex Other investigators have noted that adrenalectomy in rats does not blunt the rise in blood pressure evoked by brainstem lesions [8]

Group I acute adrenalectomy and ganglionic blockade demonstrated the beta adrenergic effect of increased cardiac output and decreased systemic resistance but essentially no alpha adrenergic effect This implies the alpha adrenergic effect is lacking because of neurogenic blockade or absent adrenal secretions Group II adrenalectomy only demonstrated that both the alpha and beta adrenergic effect occurred during elevated CSF pressure and indicated the alpha adrenergic stimulation is dependent on an intact sympathetic nervous system but is independent of the adrenal The beta adrenergic effect seems independent of both an intact sympathetic nervous system and the adrenals Since the alpha adrenergic effect of increased aortic pressure was absent in Group I (adrenalectomy and ganglionic blockade) and present in Group II (adrenalectomy) it is probably neurogenically mediated Group I (studied acutely after adrenalectomy) is not comparable to Group II (studied 17 ± 2 days after adrenalectomy) but Group I did demonstrate a beta adrenergic response of increased cardiac output and decreased peripheral resistance similar to that in animals previously studied with intact adrenals ganglionic blockade and alpha adrenergic blockade [9]

Therefore the Cushing reflex consists of a dual mechanism for the alpha adrenergic component First the adrenals are necessary to provide a vasoconstrictor agonist that affects denervated skeletal musculature (Group III A) Secondly a neurogenically mediated component is present since the alpha adrenergic effect of increased systemic blood pressure will occur in the adrenalectomized animal with intact sympathetic nervous system (Group II) but will not occur in the adrenalectomized animals with ganglionic blockade (Group I) Also in the adrenalectomized dog the innervated muscle (Group III C) responded dramatically to elevated CSF pressure with no response in the denervated preparation (Group III B)

The expected beta adrenergic effect[6, 9] of elevated cerebrospinal fluid pressure increased cardiac output or decreased systemic vascular resistance seems independent of the adrenals and the sympathetic nervous system because it is detectable in adrenalectomized dogs with or without ganglionic blockade (Groups I and II) Preliminary studies demonstrated responsiveness of the denervated gracilis muscle preparation to isoproterenol Since gracilis muscle resistance did not change with elevated CSF pressure in animals with intact adrenals and alpha adrenergic blockade (Group IV) it is assumed no significant circulating vasodilator (beta adrenergic effect) of the denervated skeletal muscle vasculature is present However total systemic vascular resistance decreased in Group I (adrenalectomy and ganglionic blockade) and also in animals previously studied with intact adrenals with and without ganglionic blockade and alpha adrenergic blockade [9] This probably reflects dilation of vascular beds other than skeletal muscle With alpha adrenergic blockade the beta adrenergic effect may only represent withdrawal of peripheral alpha adrenergic vasoconstrictor tone However a beta adrenergic effect occurred in Group I during ganglionic blockade in the absence of specific alpha adrenergic blockade

The specific origin of a circulating beta adrenergic agonist is open to speculation It is probably not neuronally released since Glick and co workers have shown that neuronally released

from the control period during 5 and 10 minutes of CSF pressure 200 mm Hg respectively In these animals with intact adrenals it is of particular interest that 21 ± 17 seconds (mean ± SD) were required for mean aortic pressure to increase to 200 mm Hg after CSF pressure was increased to 200 mm Hg In contrast 48 ± 11 seconds elapsed before any detectable increase from control was noted in the denervated gracilis muscle perfusion pressure and 4 6 ± 3 6 minutes elapsed before the gracilis muscle perfusion pressure reached a maximum

In the animals with beta adrenergic blockade denervated gracilis muscle preparation and adrenalectomy (Group III B) control aortic pressure (131 ± 4 mm Hg) increased significantly during 5 minutes CSF pressure 200 mm Hg There was no significant change in the resistance of the denervated gracilis muscle

In Group III C (beta adrenergic blockade adrenalectomy innervated gracilis muscle), control aortic pressure (125 ± 19 mm Hg) increased significantly during 5 minutes CSF pressure 200 mm Hg Gracilis muscle resistance increased significantly during 5 and 10 minutes CSF pressure 200 mm Hg The aortic pressure and gracilis muscle resistance began to increase about the same time (18 to 30 seconds) after CSF pressure was increased to 200 mm Hg Aortic pressure usually reached a maximal value in 14 to 64 seconds whereas the gracilis muscle resistance showed a progressive increase over 3 to 4 5 minutes up to 10 minutes

Group IV alpha adrenergic blockade and intact adrenals aortic pressure demonstrated a significant decrease during 5 and 10 minutes of CSF pressure 200 mm Hg from 105 ± 13 mm Hg in the control period There was no change in resistance of the gracilis muscle

Arterial blood for all dogs in the control period demonstrated pH 7 39 ± 0 03 $PaCO_2$ 40 ± 3 mm Hg and PaO_2 87 ± 7 mm Hg At the conclusion of 10 minutes CSF pressure 200 mm Hg arterial blood showed pH 7 33 ± 0 04 $PaCO_2$ 41 ± 5 mm Hg and PaO_2 83 ± 8 mm Hg

Discussion

Cushing in 1901[1] demonstrated a pressor response to elevated intracranial pressure Subsequent investigators considered several mechanisms including a humoral vasopressor in the chick[11] cerebral ischemia[4 14] venoconstriction[13] neurohumoral stimulation with a phasic response of systemic blood pressure in dogs and rabbit myocardial inotropic response[1] and shunting[1] Mechanical compression of the rat brain produces a pressor response not altered by adrenalectomy or bilateral cervical vagotomy[1] A receptive area in the lower brainstem possibly mediates the Cushing response In 1970 the Cushing response (reflex) was clearly separated into alpha and beta adrenergic components This study was initiated to determine the etiology of these alpha and beta effects

The animals with the denervated and perfused gracilis muscle preparation beta adrenergic blockade and intact adrenals (Group III A) demonstrated an increase in resistance of the gracilis muscle preparation indicating a circulating vasoconstrictor of skeletal muscle The aortic pressure also increased significantly and could be caused by either a humoral agonist or neurogenic stimulation The significant time lag between aortic pressure elevation and elevation of the gracilis muscle perfusion pressure is indicative of a circulating vasoconstrictor that is delayed by the external pump that perfuses the gracilis muscle preparation

In contrast the animals with the denervated perfused gracilis muscle preparation beta adrenergic blockade and no adrenals (Group III B) demonstrated an increased aortic pressure but no change in gracilis muscle perfusion pressure or resistance Therefore the adrenals appear to be the source of the alpha adrenergic agonist affecting the denervated gracilis muscle since any increase in resistance of the gracilis muscle is absent in the adrenalectomized dog with beta adrenergic blockade The increase in aortic pressure in both Group III A and B is probably neurogenic and nonadrenal in origin

The neurogenic component of the Cushing reflex is demonstrated in Group III C (no adrenals beta adrenergic blockade and innervated gracilis muscle) In contrast to the lack of change in the denervated gracilis muscle resistance in Group III B Group III C demonstrated a marked increase in gracilis muscle resistance

Group I animals with ganglionic blockade studied acutely after adrenalectomy demonstrated changes similar to those previously reported in animals with intact adrenals ganglionic blockade and alpha adrenergic block

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norepinephrine does not have access to beta adrenergic receptors in contrast to injected norepinephrine Although the reuptake of neuronally released norepinephrine may be inhibited by phenoxybenzamine, it is doubtful this permits access of neuronally released norepinephrine to beta adrenergic receptors It is also possible some autonomic pathways are invulnerable to ganglionic blockade An adrenal source seems excluded by the present study but brain amines or nonadrenal chromaffin tissue might be a consideration

A dopaminergic response is an unlikely explanation for the Cushing response since alpha and beta adrenergic antagonists are relatively ineffective in blocking this response Parasympathetic activity is reasonably excluded since gallamine triethiodide has significant vagolytic effects Intravenous propranolol in dogs 0 2 to 0 25 mg / Kg effectively blocks changes induced by isoproterenol However in addition to beta receptor blocking properties propranolol has nonspecific effects that would be similar in Group III A B and C

Summary

The cardiovascular effects of elevated cerebrospinal fluid (CSF) pressure were studied in adrenalectomized dogs with and without ganglionic blockade A significant increase in vascular pressures and cardiac output occurred in those without ganglionic blockade but was absent or markedly blunted in those with ganglionic blockade This indicated that an intact sympathetic nervous system was required for the pressor response to elevated cerebrospinal fluid pressure but the adrenals were not required A beta adrenergic effect was noted in dogs with ganglionic blockade and adrenalectomy

The effects of elevated CSF pressure were also studied using a perfused gracilis muscle preparation in 12 animals with beta adrenergic blockade with and without adrenalectomy Animals with intact adrenals and denervated gracilis muscle showed an increase in aortic pressure and gracilis muscle resistance Adrenalectomized animals with innervated gracilis muscle demonstrated an increase in aortic pressure and gracilis muscle resistance Elevated CSF pressure with intact adrenals and alpha adrenergic blockade demonstrated a decrease in aortic pressure but no change in gracilis muscle resistance

The presence of a nonadrenal circulating beta agonist that increases cardiac output and decreases peripheral vascular resistance is indicated by these studies Also the Cushing reflex involves an adrenal alpha adrenergic component affecting skeletal muscle resistance and another alpha adrenergic component dependent on an intact sympathetic nervous system

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norepinephrine does not have access to beta adrenergic receptors in contrast to injected norepinephrine Although the reuptake of neuronally released norepinephrine may be inhibited by phenoxybenzamine [8] it is doubtful this permits access of neuronally released norepinephrine to beta adrenergic receptors It is also possible some autonomic pathways are invulnerable to ganglionic blockade An adrenal source seems excluded by the present study but brain amines or nonadrenal chromaffin tissue might be a consideration

A dopaminergic response is an unlikely explanation for the Cushing response since alpha and beta adrenergic antagonists are relatively ineffective in blocking this response Parasympathetic activity is reasonably excluded since gallamine triethiodide has significant vagolytic effects [ ] Intravenous propranolol in dogs 0 2 to 0 25 mg / Kg effectively blocks changes induced by isoproterenol [ ] However in addition to beta receptor blocking properties propranolol has nonspecific effects that would be similar in Group III A B and C [ ]

Summary

The cardiovascular effects of elevated cerebrospinal fluid (CSF) pressure were studied in adrenalectomized dogs with and without ganglionic blockade A significant increase in vascular pressures and cardiac output occurred in those without ganglionic blockade but was absent or markedly blunted in those with ganglionic blockade This indicated that an intact sympathetic nervous system was required for the pressor response to elevated cerebrospinal fluid pressure but the adrenals were not required A beta adrenergic effect was noted in dogs with ganglionic blockade and adrenalectomy

The effects of elevated CSF pressure were also studied using a perfused gracilis muscle preparation in 12 animals with beta adrenergic blockade with and without adrenalectomy Animals with intact adrenals and denervated gracilis muscle showed an increase in aortic pressure and gracilis muscle resistance Adrenalectomized animals with innervated gracilis muscle demonstrated an increase in aortic pressure and gracilis muscle resistance Elevated CSF pressure with intact adrenals and alpha adrenergic blockade demonstrated a decrease in aortic pressure but no change in gracilis muscle resistance

The presence of a nonadrenal circulating beta agonist that increases cardiac output and decreases peripheral vascular resistance is indicated by these studies Also the Cushing reflex involves an adrenal alpha adrenergic component affecting skeletal muscle resistance and another alpha adrenergic component dependent on an intact sympathetic nervous system

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of 30 mg /Kg and it was placed in oxygenated Tyrode s solution composed of (mM) NaCl 147 KCl 4 0 CaCl 1 8 MgCl 0 5 dextrose 5 5 NaH PO 1 5 Na HPO 4 5

Preparations of both the LBB and RBB systems obtained from the canine heart were immersed in a single tissue bath The chamber was perfused with Tyrode s solution equilibrated with 100 per cent O_2 The temperature of the bath was kept between 36 and 36 5 C

Transmembrane action potentials were recorded through machine pulled glass microelectrodes filled with 3M KCl and having resistances between 10 and 30 megohms Signals from the microelectrodes were fed to amplifiers (MZ 4 Nihonkoden and M701 W P Instruments Inc) and the outputs of these amplifiers were displayed on oscilloscopes (VC 7 Nihonkoden and 5103N Tektronix) The transmembrane signals were recorded photographically from the oscilloscope screens

Tissue preparations Fig 1 shows the preparations of the LBB and RBB systems (stained with Lugol s solution) used in the current experiments The specimen of the LBB system is shown in the upper panel of the figure The main left bundle emerges with a band like structure below the aortic ring and it courses down the septum a few millimeters before the main LBB bifurcates into the anterior (AF) and posterior fascicles (PF) which are attached to the apical portions of the papillary muscles A profuse subendocardial network of the mid septal Purkinje fibers (SEP) is distributed throughout the septal surface bordered by two major fascicles

The preparation of the RBB system consists of the main RBB in the right upper septum and its subsequent two or three false tendons which terminate in the free wall (*lower panel* Fig 1) To study APD and refractory periods along this pathway on the right side of the conduction system the right ventricular septal muscle was separated from the free wall or anterior papillary muscle (PM) As shown in diagrams of the RBB specimen in Figs 2 and 3 consequently these muscle masses were bridged by a single strand of the RBB

Stimulation of the preparations In each experiment a pair of preparations of the right and left conducting systems obtained from a dog heart were stimulated simultaneously using the same stimulator through two pairs of bipolar electrodes

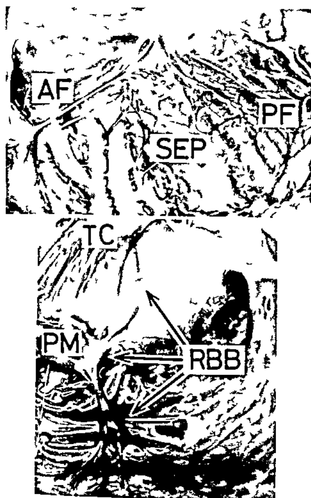


Fig 1 A pair of preparations of the left bundle branch system (*top panel*) and right bundle branch system (*bottom panel*) isolated from the same canine heart (stained with Lugol s solution) In the specimen from the LBB (*top*) the septal muscle was rather large (about 3 × 5 cm) and it included the septal Purkinje fibers (*SEP*) the anterior (*AF*) and posterior (*PF*) fascicles The RBB specimen (*bottom*) consisted of the main RBB with its attached septal muscle and false tendons which terminated in ventricular free wall *RBB* = right bundle branch *TC* = tricuspid valve *PM* = anterior papillary muscle

on each proximal portion of the RBB and LBB The specimens were driven at a basic cycle length of 750 msec (80 times/minute) using a driving stimulus (S1) which was two times the diastolic threshold in intensity and 3 msec in duration

In order to determine the functional refractory period (FRP) a test stimulus (S2) was delivered through the same electrodes after every eighth driving stimulus The minimum interval between the response (R1) to S1 and the response (R2) to S2 was defined as the FRP in each of the right and left ventricular conduction systems

Functional properties of the left septal Purkinje network in premature activation of the ventricular conduction system

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In relatively recent in vivo or in vitro experiments on the canine heart[1-5] several investigators have suggested that the left bundle branch (LBB) system has three rather than two separate divisions, i.e., a trifascicular concept of the left conducting system consisting of the septal Purkinje fibers besides the anterior (AF) and posterior (PF) fascicles. Very lately, in addition, Lazzara and co-workers[6] have reported that the septal Purkinje fibers of the LBB system, which were termed interior fibers by them, have significantly shorter action potential durations (APD) and refractory periods than the right bundle branch (RBB), the AF and PF of the LBB system. In the series of our experiments apart from the work of Lazzara and colleagues,[6] we compared the APD (80 per cent of repolarization time) and functional refractory period (FRP) between the canine left and right conduction systems in order to elucidate the electrophysiological mechanism underlying aberrant ventricular conduction. As the result of our experiments in agreement with their study,[6] we have found that both the APD and the FRP of the mid-septal Purkinje fibers in the LBB system are significantly shorter than those of the other three conduction pathways, and have reported previously[7] that the electrophysiological properties of the septal Purkinje fibers might contribute to the higher incidence of RBB block in ventricular aberrant conduction of supraventricular premature beats.

Since, however, septal Purkinje fibers near the main LBB could not be clearly differentiated from conducting fibers of the AF and PF in the subendocardium, which were named anterior and posterior border fibers by Lazzara and colleagues, it seemed quite essential to confirm the functional independence of the septal Purkinje network serving as a conduction pathway for premature impulses delivered to the main LBB. In the present study, therefore, we elucidated the premature activation sequences of the left conducting tissue and ordinary ventricular muscle when premature stimuli were applied to the main LBB using a relatively large preparation including all three major pathways of the left conduction system. As a result, it has been demonstrated that the septal Purkinje fibers have functional significance for conduction of premature impulses and there are not such definite gate cells in this pathway as Myerburg and colleagues[8] have proposed previously.

Methods

Experiments were performed on isolated cardiac tissue obtained from mongrel dogs. The heart was removed from the dog after anesthetizing it with sodium pentobarbital administered at a rate

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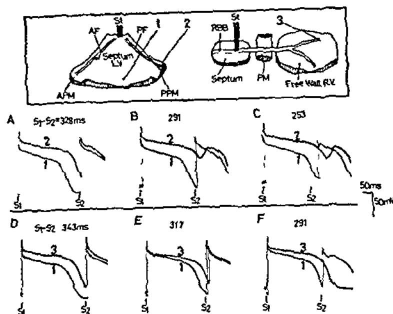


Fig 3 Discrepancies of premature responses of Purkinje fibers between the LBB and RBB systems Action potentials were recorded from three sites (1) the lower third of the left ventricular central septum (2) the terminations of the PF and (3) the RBB Action potentials of driven and premature responses were recorded simultaneously from the sites of (1) and (2) (panels A B and C) and from the sites of (1) and (3) (panels D E and F) at various coupling (S S) intervals Note that the premature response of the septal Purkinje fiber was elicited at an S S interval of 253 msec though the terminal Purkinje cells of the PF and the RBB responded only abortively or did not respond to test stimuli at longer coupling intervals.

thereafter they form the false tendons (solid lines) which terminate in ventricular muscle In these conduction pathways we observed a progressive lengthening of APD with increasing distance from the main bundle branches to the false tendons and an area of maximum APD (max APD) was found at the false tendon On the other hand the septal Purkinje fibers of the LBB system (SFP) are blanketing the subendocardium from the origin to their termination in ventricular muscle (interrupted line) In this specimen there was a tendency to shorter durations with distance progression along the approximately intermediate septal surface between the AF and PF As a general rule however it was almost impossible to clearly discriminate the septal Purkinje fibers from conducting fibers of the AF or PF within several millimeters from the main LBB Although there was a trend toward longer durations of action potentials recorded from the interior septal surface along the AF and PF the septal Purkinje fibers had apparently shorter action potentials than the other three conduction pathways at almost all sites approximately equidistant from the main bundle branches

In a total of 18 experiments, we compared the

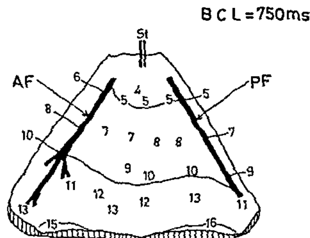


Fig 4 An isochronic map showing the sequence of normal activation of the left conducting system The left preparation was driven at a basic cycle length (B C L) of 750 msec through a pair of bipolar surface electrodes (St) on the main LBB Numbers in the diagram indicate activation times (msec.) of the Purkinje fiber

maximum APD (max APD) among the four conduction pathways in a pair of the left and right specimens which were isolated from the same canine heart The results are shown in the left column of Table I The number of experi

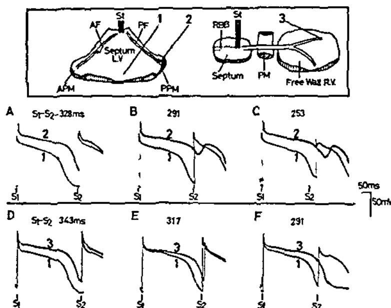


Fig. 3. Disparities of premature responses of Purkinje fibers between the LBB and RBB systems. Action potentials were recorded from three sites: (1) the lower third of the left ventricular central septum, (2) the terminations of the PF, and (3) the RBB. Action potentials of driven and premature responses were recorded simultaneously from the sites of (1) and (2) (*panels A, B and C*) and from the sites of (1) and (3) (*panels D, E and F*) at various coupling (S1-S2) intervals. Note that the premature response of the septal Purkinje fiber was elicited at an S1-S2 interval of 253 msec, though the terminal Purkinje cells of the PF and the RBB responded only abortively or did not respond to test stimuli at longer coupling intervals.

thereafter they form the false tendons (solid lines) which terminate in ventricular muscle. In these conduction pathways we observed a progressive lengthening of APD with increasing distance from the main bundle branches to the false tendons and an area of maximum APD (max APD) was found at the false tendon. On the other hand, the septal Purkinje fibers of the LBB system (SFP) are blanketing the subendocardium from the origin to their termination in ventricular muscle (*interrupted line*). In this specimen there was a tendency to shorter durations with distance progression along the approximately intermediate septal surface between the AF and PF. As a general rule, however, it was almost impossible to clearly discriminate the septal Purkinje fibers from conducting fibers of the AF or PF within several millimeters from the main LBB. Although there was a trend toward longer durations of action potentials recorded from the interior septal surface along the AF and PF, the septal Purkinje fibers had apparently shorter action potentials than the other three conduction pathways at almost all sites approximately equidistant from the main bundle branches.

In a total of 18 experiments, we compared the maximum APD (max APD) among the four conduction pathways in a pair of the left and right specimens which were isolated from the same canine heart. The results are shown in the left column of Table I. The number of experi-

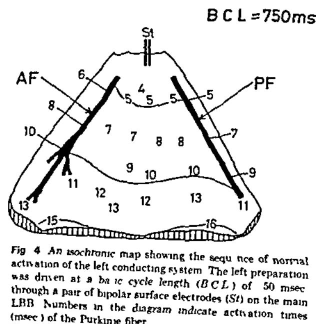


Fig. 4. An isochronic map showing the sequence of normal activation of the left conducting system. The left preparation was driven at a basic cycle length (*BCL*) of 750 msec through a pair of bipolar surface electrodes (*St*) on the main LBB. Numbers in the diagram indicate activation times (msec) of the Purkinje fiber.

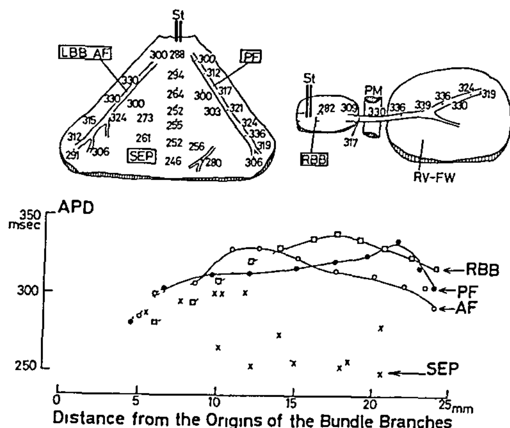


Fig 2 Action potential durations (*APD*) of Purkinje fibers mapped along the courses of a pair of preparations of the LBB and RBB systems *In upper panels numbers in the diagrams indicate 80 per cent level of repolarization* time in msec *In the lower panel* the graph was drawn to represent a relation between the values of APD obtained and distance (mm) of recording sites from the origins of the bundle branches on the ventricular septal surface APD measured at the subendocardial Purkinje fiber was connected by interrupted lines and APD at the false tendon was linked by solid lines At almost all comparable levels in the ventricular conducting systems the APD of the septal Purkinje fibers (*SEP*) of the LBB system (*marked by x*) was consistently shorter than that of the RBB (*open square*) the AF (*open circle*) and the PF (*filled circle*) of the LBB system *LBB AF* = the anterior fascicle of the LBB system *PF* = the posterior fascicle *SEP* = the septal Purkinje fibers *RV FW* = free wall of the right ventricle *St* = bipolar electrodes for stimulation

In the left preparation stimulation of the Purkinje fiber in the main LBB devoid of the adjacent muscle was confirmed (Figs 4 and 6*A*) Stimulation (St) delivered through a pair of bipolar surface electrodes on the origin of the LBB allowed propagation of activation of Purkinje fibers from base to apex along the AF PF, and septal Purkinje network (Fig 4) The earliest muscle activation on the other hand was approximately at the lower third of the septum between the papillary muscles and the general sequence of the ordinary ventricular muscle was from apex to base (Fig 6*A*)

Results

Comparison of action potential durations between the LBB and RBB systems In each of 18 experiments, action potentials of Purkinje fibers were recorded from 15 to 20 points along each of the courses of the following four conduction pathways in a pair of the left and right specimens which were obtained from the same canine heart (1) the conduction pathway consisting of the main RBB and its subsequent false tendons which terminate in the ventricular free wall (RBB), (2) the anterior fascicle of the LBB system (LBB AF) (3) the posterior fascicle (LBB PF) and (4) the septal Purkinje fibers on the left septal surface between the AF and PF (LBB SEP) Fig 2 shows action potential durations (APD) obtained in this way in a pair of typical preparations In the upper panel of this figure numbers in diagrams of the specimens indicate APD (msec) The values of the APD are plotted against distance (mm) from the origin of the bundle branch on the surface of the interventric ular septum (*lower panel* Fig 2) The RBB AF and PF of the LBB system are subendocardial structures (interrupted lines in the lower graph of Fig 2) within 5 to 15 mm from their origins and

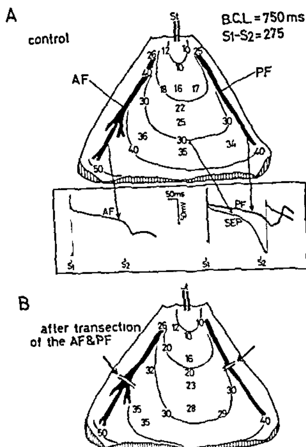


Fig 5 An isochronic map showing the sequence of premature activation of the left conducting tissue in the same specimen as Fig 4 indicated (*panel A*) Numbers in the diagram indicate activation times (msec) of the Purkinje fiber in response to a premature impulse (S) delivered to the main LBB at an S S interval of ? 5 msec which was nearly equal to refractory periods of the AF and PF The sequence of Purkinje activation was from base to apex along the midseptum Records in insets show driven and premature action potentials of the AF the PF and the septal Purkinje fiber at this critical coupling interval *Panel B* shows the premature activation sequence of the conducting fibers at the same S S interval after transection of the false tendons of the AF and PF The incision of these fascicles produced no significant changes in premature activation times.

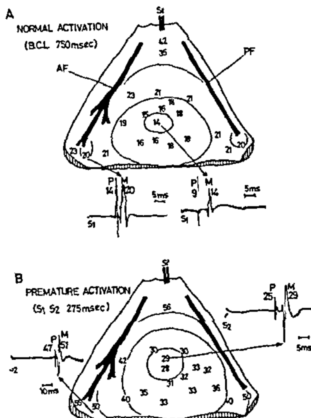


Fig 6 Sequential activation of muscle cells of the septal surface in response to a basic stimulus (S1) (*panel A*) and a premature stimulus (S2) having a coupling interval of 275 msec (*panel B*) Numbers in the diagrams indicate activation times (msec) after stimulation The earliest muscle activation was observed at approximately the same region (middle or lower third of the central septum) in both normal and premature activation of the LBB system *Records below and at the sides* show bipolar surface electrograms from the anterior papillary muscle and an area at which the initial muscle activation was observed *P* = Purkinje activation M = muscle activation

delay of conduction (42 msec) even at an S S interval of 2?3 msec and repolarization of this cell was still nearly complete (*panel C* Fig 3) As shown in the lower recordings of Fig 3 the terminal Purkinje fiber in the RBB responded to the premature impulse until a coupling interval was shortened to 317 msec (*panels D* and *E* Fig 3) The premature response of the cell no longer occurred at an S S interval of 291 msec (*panel F* Fig 3)

Functional properties of the septal Purkinje fibers in premature activation of the LBB system

Using a pair of close bipolar electrodes we measured the activation time of the Purkinje fiber at about 40 points in the left preparation while the main LBB was driven at a basic cycle of 750 msec (80 times/minute) In the isochronic map indicating the normal activation sequence as shown in Fig 4 the left conducting tissue was activated from base to apex forming concentric wave fronts along the major fascicles (the AF and PF) and the septal Purkinje network Since there were significant differences in the FRP between the septal Purkinje fiber and the false tendons of the AF and PF as shown in Table I the prema

Table I Comparison of the maximum APD (max APD) and the FRP between the left and right conduction pathways

	max APD	*FRP*
	(N = 16)	(N = 16)
RBB	337	332
LBB SEP	302	300
Mean difference	35 ± 19*	32 ± 14
	(N = 9)	(N = 9)
LBB AF	323	315
LBB SEP	301	289
Mean difference	22 ± 8*	26 ± 14*
	(N = 15)	(N = 13)
LBB PF	341	336
LBB SEP	302	297
Mean difference	39 ± 17*	39 ± 19

Values are mean (± SD) msec of the number of preparations studied (number in parentheses)
* $P < 0.005$ (Student's t test)
Abbreviations max APD = the maximum value of action potential durations mapped along the courses of the conduction pathways FRP = the functional refractory period of the Purkinje fiber measured at the terminations of the conduction pathways RBB = the right bundle branch LBB SEP = the septal Purkinje fiber of the left bundle branch system LBB AF = the anterior fascicle LBB PF = the posterior fascicle

ments shown (in parentheses) differs because action potentials were recorded from only two or three pathways in several preparations As shown in the first comparison, the mean values of the max APD of the RBB and the septal Purkinje fiber of the LBB system (LBB SEP) were 337 and 302 msec respectively, and the mean difference in each experiment was 35 ± 19 (± SD) msec In addition the max APD of the septal Purkinje fiber was significantly shorter than that of the AF and PF of the LBB system and the mean differences were 22 ± 8 and 39 ± 17 msec respectively These differences (asterisks in Table I) were statistically significant ($p < 0.005$ Student's t test) However we did not find any meaningful difference in the max APD between the RBB and the AF and the PF (these comparisons were omitted in Table I)

Comparison of functional refractory periods between the LBB and RBB systems Using the same specimens as were used to measure APD we determined the FRP at the following four sites in the RBB and LBB systems the terminations of (1) the RBB (2) the AF and (3) the PF of the LBB system and (4) the lower surface of the midseptum nearly intermediate between the AF and PF Since the earliest muscle activation was observed approximately at the junction of the middle and lower thirds of the midseptum (Fig 6A) and the septal Purkinje fiber was therefore assumed to terminate in the ordinary ventricular muscle at this particular region the FRP of the septal Purkinje fiber was measured at the above mentioned site in the septum Comparison of the FRP was made among the four conduction pathways in the same way as that of the max APD The right column of Table I represents the results There was a close relation between each value of the FRP at the four conduction pathways and the max APD of the corresponding courses The FRP of the septal Purkinje fiber of the LBB system was significantly ($p < 0.005$) shorter than that of the terminal Purkinje cells in the RBB the AF and PF of the LBB system However we found no significant differences in the FRP among the false tendons of the RBB the AF, and PF

It was suggested that these differences in refractory periods among the pathways would result in significant disparities in premature responses of Purkinje fibers between the left and right conducting systems Fig 3 shows that this is true As indicated in the diagrams action potentials of Purkinje fibers were recorded from three sites in a pair of specimens which were stimulated simultaneously by the same stimulator the lower third of the left ventricular septum (site 1) the terminations of the PF of the LBB system (site 2) and of the RBB (site 3) At various S_1 S intervals the action potentials of driven and premature responses were recorded simultaneously from the Purkinje fibers in the lower septum and the PF (panels *A* *B*, and *C* Fig 3) and from the cells in the lower septum and the RBB (*panels D E* and *F* Fig 3)

At an S_1 S interval of 328 msec both the cells in the lower septum and the termination of the PF fully responded to the test impulse (S2) without any delay of conduction of the premature impulse (*panel A*, Fig 3) At a coupling interval of 291 msec however, the premature action potential of the cell in the PF showed a slow upstroke with some delay of conduction of the test impulse On the other hand the septal Purkinje fiber was almost fully repolarized at that time and appropriately responded to S2 without any significant delay (*panel B* Fig 3) The cell in the lower septum responded to the test impulse with some

the APD and FRP were compared between the LBB and RBB systems As a result we have found that the maximum APD and the FRP of the septal Purkinje fibers in the LBB system are significantly shorter than those of the RBB the AF and PF of the LBB system (Table I) These results are in accord with the recent study performed by Lazzara and colleagues They therein reported that there was a tendency to longer durations of action potentials of interior fibers (septal Purkinje fibers) of the LBB system with distance progression though they observed somewhat greater variability in the APD among these fibers In our 18 preparations we also observed that the APD of the septal Purkinje fiber greatly varied among recording sites on the septal surface However we found no consistent relation between the APD of the septal Purkinje fiber and distance of recording sites from the main LBB in the majority of specimens though there was a general tendency to shorter durations of these fibers with increasing distance from the proximal LBB along the approximately intermediate septal surface between the AF and PF in six of 18 preparations as shown in Fig 2 Such inconsistency between our result and their report seems to be related to the following matters First it was almost impossible to differentiate the septal Purkinje fibers from the conducting fibers originated from the AF and PF near the proximal LBB since the septal Purkinje fibers are confluent with the subendocardial Purkinje cells of the AF and PF which have been termed the anterior and posterior border fibers by them[4] forming a fan shaped structure on the upper septum below the main LBB Therefore it seems possible that action potentials recorded from the upper septum are actually those of conducting fibers originated from the AF or PF In most of our preparations (11 out of 18) moreover we observed a general tendency to longer APD at the interior septal surface along the false tendons of the AF and PF than at the central septum This variation of APD may be ascribed to a rather dense distribution of conducting fibers which branch off directly from the two fascicles Secondly a profuse network of septal Purkinje fibers consisted of innumerable branches having various thicknesses and sizes from fine thread to strand like structures after specimens were stained with iodine As a general tendency we found longer APD in rather thicker branches than in nearby cells in very thin networks with the aid of a dissecting microscopy In addition longer durations were often obtained from the false tendon like structure which was formed by septal Purkinje fibers occasionally even on the midseptum Thus greater variability in APD among recording sites on the septal surface seems to result from such an irregular architecture of the septal Purkinje fibers as described above

Combining these observations it has been suggested that these septal Purkinje cells have a very complex distribution showing rich interconnections with fibers originated from the AF and PF especially in the vicinity of the main LBB and the interior septal surface along the two fascicles Therefore it seemed quite indispensable to confirm (1) the functional independence of the septal Purkinje fibers as a conduction pathway for premature impulses in spite of such a complex and irregular architecture of these fibers and (2) the lack of such gate cells in this conduction pathway as Myerburg and colleagues[4, 5] have brought forward For these purposes we elucidated the activation sequences of the left conducting tissue and ordinary ventricular muscle of the septal surface in response to a premature impulse delivered to the main LBB at a critical coupling interval close to the refractory periods of the AF and PF In this experiment we observed that the earliest muscle activation by the test impulse occurred at the same area near the junction of the middle and lower thirds of the septum as in normal activation of the LBB system and that the intervals between Purkinje and muscle activation in bipolar surface electrograms recorded from this particular area were almost constant under these two conditions (Fig 6) Thus it has been demonstrated that the septal Purkinje network provides the quickest pathway for conduction of premature impulses to the septal myocardium and moreover that there is no definite distal gate in this pathway

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ture activation sequence of the LBB system by the test impulse having a critical coupling interval close to the refractory periods of these fascicles was expected to differ from the normal activation sequence. At an S_1-S_2 interval of 275 msec., which was nearly equal to the refractory periods of the AF and PF, the premature activation time of the left conducting fiber was mapped in the same specimen as Fig. 4 indicated (Fig. 5*A*). As shown in this figure, the Purkinje fiber on the left septal surface was activated nearly along the midseptum from the proximal LBB to the apex with additional conduction delay (5 to 35 msec.) of the test impulse (S2) compared with the normal activation shown in Fig. 4. At that time we observed marked delay of conduction of the premature impulse in the major fascicles. In order to verify disparities of premature responses between the septal Purkinje fiber and these false tendons, action potentials were recorded from the terminal Purkinje fibers of the AF and PF and from the septal Purkinje cell in the lower midseptum (insets of Fig. 5). The premature action potential of the AF showed only a minor hump-like response and that of the PF an abortive depolarization with pronounced conduction delay of the test impulse (S2). On the other hand, the premature response of the septal Purkinje fiber showed a nearly full-sized depolarization rising from the deeper level of the membrane potential, resulting in smaller conduction delay (20 msec.) of S2.

In order to give some definite evidence of the functional significance of the septal Purkinje fibers, after transection of the AF and PF we constructed an isochronic map showing the sequence of premature activation of the left conducting tissue in the same specimen (Fig. 5*B*). The cutting of these two false tendons produced no significant changes in premature activation times of conducting cells even at the papillary muscles in which the major fascicles terminated. At this critical coupling interval (275 msec.), therefore, the premature impulse was propagated over the entire septal surface through the septal Purkinje network.

Furthermore, we elucidated the sequences of normal and premature activation of ordinary ventricular muscle of the septal surface in the same specimen (Fig. 6). In response to a driving stimulus (S1) delivered to the main LBB, the earliest muscle activation was observed at the junction of the middle and lower thirds of the midseptum (14 to 15 msec. after S1) and the myocardium of the septal surface was activated in the form of concentric bands around this island. On the other hand, muscle activation at the papillary muscles was observed relatively early (20 to 23 msec. after stimulation) (Fig. 6*A*). Fig. 6*B* represents the sequence of muscle activation by the test impulse (S2) having an S-S interval of 275 msec. The initial activation of the septal muscle was observed 28 to 30 msec. after S2 at almost the same area as in normal activation and the muscle activation spread over the entire septal surface forming concentric lines. The papillary muscles, consequently, were activated very late (50 to 55 msec. after S2) compared with normal activation. From these results it was apparent that the septal Purkinje fibers provided the quickest pathway for conduction of the test impulse to the septal myocardium at this critical coupling interval. In the false tendons of the AF and PF, however, conduction of the premature impulse was accompanied by marked delay because of their longer refractoriness. Thus these fascicles did not function effectively as conduction pathways for S2 at this coupling interval.

Discussion

Many investigators[1-6] have reported that the LBB system consists of three major conduction pathways ("trifascicular system"). Lazzara and colleagues[1] studied the activation sequences of the left conducting tissue and septal myocardium before and after transection of the proximal LBB using rather large specimens isolated from the canine left ventricle. This study indicated the functioning of the septal Purkinje fibers as an independent pathway from the AF and PF in physiological conditions. Several experiments on in vivo canine hearts[7-9] suggested that the activation of the left ventricular muscle of the septum is initiated by propagated impulses predominantly through the septal Purkinje fibers. In addition, an anatomical study[10] on the canine ventricular special conduction system showed the trifascicular system of the LBB system consisting of the anterior and posterior primary branches and a vast network of fibers extending between the major branches in the LBB system.

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transection of the lateral branches (false tendons) resulted in incomplete BRR block patterns This study has suggested that the anterior septal or posterior branches of the RBB have much less functional significance as conduction pathways in physiological conditions compared with a dense distribution of lateral branches on the right ventricular free wall In our experiments, conse quently, we did not record action potentials from these smaller ramifications of the anterior septal or posterior branches though the APD and FRP were measured at the main RBB and its subse quent false tendons

In the isolated human heart Durrer and co workers[1] have elucidated three sites of the left ventricle at which the earliest muscle activation is observed suggesting the functioning of three major conduction pathways in the LBB system Thus, if our results obtained from the canine heart can be to some degree extrapolated to the human heart, the higher incidence of aberrant conduction with an RBB block pattern in the majority of clinical electrocardiograms may be attributed to shorter refractory periods of the septal Purkinje fibers in the human heart also Also, since differences in refractory periods[13] between the septal Purkinje fibers of the LBB system and the RBB tend to increase at slow heart rates, aberrant conduction of supraventric ular premature beats following longer preceding periods is likely to result in complexes showing an RBB block configuration

A recent anatomical study[14] on the specialized conduction system of the human heart has indi cated the presence of the mid septal Purkinje fibers and moreover, the extreme variability of these fiber groups especially in the proximal portion of the LBB In agreement with this study, we observed a rather poorly developed distribu tion of the septal Purkinje fibers near the prox imal LBB in some preparations If the septal Purkinje network can not function effectively as a conduction pathway for premature impulses due to such variety of distribution of these fiber groups as mentioned above various patterns of aberrancy in the QRS[15] may be brought on in addition to the typical configuration of RBB block in the human heart

Summary

To elucidate the mechanism underlying ven tricular aberrant conduction, in each of 18 experi ments we measured action potential durations (APD) and functional refractory periods (FRP) of the Purkinje fiber along the following four conduction pathways in a pair of the right and left specimens isolated from the same canine heart (1) the right bundle branch (RBB) and its subsequent false tendon, (2) the anterior fascicle (AF), (3) the posterior fascicle (PF), and (4) the septal Purkinje fiber of the left bundle branch (LBB) system Both the APD and the FRP of the septal Purkinje fiber on the left septal surface were significantly shorter than those of the RBB the AF, and PF of the LBB system, though we found no meaningful differences in the APD and the FRP among the false tendons of the RBB the AF, and PF It was thus suggested that the electrophysiological properties of the septal Purkinje fiber might have functional significance in premature activation of the LBB system In order to verify this hypothesis furthermore we studied the sequential activation of the left conducting tissue and muscle cells of the left septal surface, applying a premature stimulus to the main LBB at a critical coupling interval which was nearly equal to the refractory periods of the AF and PF The test impulse was propa gated to the entire septal surface through the septal Purkinje fiber resulting in the initial muscle activation at almost the same area of the middle or lower third of the midseptum as in normal activation of the LBB system The result indicates that the septal Purkinje network func tions as the quickest pathway for conduction of premature impulses to the septal myocardium and suggests that the functional properties of this fiber group contribute to the higher incidence of RBB block in ventricular aberrant conduction of supraventricular premature beats

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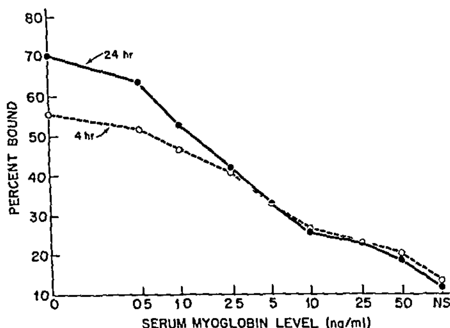


Fig 1 Standard curves utilizing the 4-*(broken line)* and 24 hour *(solid line)* radioimmunoassay determinations for serum myoglobin

and the serum sample to be tested the tubes were placed on a shaker in a cold room at 4° C for 4 hours Separation of bound from free myoglobin was then accomplished utilizing 50 per cent ammonium sulfate to precipitate the bound myoglobin Precipitates were subsequently counted as described previously

Sera were obtained from patients complaining of chest pain who were seen in the Emergency Room at Parkland Memorial Hospital in Dallas Texas during July and August 1976 (Table I) Sera were also obtained from 14 patients with renal failure who were being treated at Parkland Memorial Hospital Verbal informed consent was obtained for the venous blood collections All patients sera were stored at –20° C until they were assayed

Results

Typical standard curves utilizing both the 4 and 24 hour radioimmunoassay methods for determination of serum myoglobin were performed simultaneously with each set of patient samples that were analyzed (Fig 1) Five additional standard curves were run on different days utilizing both methods and the results obtained on each occasion were essentially identical A concentration of 0 5 ng per tube (2 5 ng /ml) was detected by both the 4 and 24 hour methods

Precision reproducibility specificity Each sample was run in triplicate and the results agreed within 3 per cent Four determinations were run on different days on a sample of normal human sera with the coefficient of variation being 3 per cent for the 24 hour test and 18 per cent for the 4 hour test In every instance if a patient s serum sample had a high myoglobin value it was high in both the 4 and 24 hour assays The specificity of the assay for myoglobin has previously been documented as has the lack of cross reactivity with other plasma and intracellular proteins[1] The data indicate that the 4 hour radioimmunoassay for determination of serum myoglobin is a specific and accurate test for measuring myoglobin levels

All sera tested were found to have detectable myoglobin levels In 53 individuals complaining of chest pain but without subsequent clinical evidence of acute myocardial infarcts the average serum myoglobin value determined by 4 hour radioimmunoassay was 33 8 ng /ml (Fig 2) Only two patients evaluated in this group had serum myoglobin values above 85 ng /ml one had unstable angina pectoris and had been drinking

Detection of myoglobin by radioimmunoassay in human sera Its usefulness and limitations as an emergency room screening test for acute myocardial infarction

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We have previously described the development of a radioimmunoassay for the measurement of serum myoglobin values and have indicated that serum myoglobin determinations utilizing this method are of value in patients in detecting the presence of acute myocardial infarcts[1] This determination previously required a 24 hour incubation time between labeled antigen and anti body prior to being able to determine serum myoglobin values[1] The relatively long time period required for the determination of serum myoglobin values by radioimmunoassay pre cluded using the test as a possible screening test' for the presence of myocardial infarction in the Emergency Room Therefore we have further modified the assay so that determinations of serum myoglobin can be made within 4 hours We have utilized this shorter radioimmunoassay to test whether serum myoglobin measurements might be used to detect the presence or absence of myocardial infarction in the Emergency Room in patients presenting with chest pain In addition we have also utilized this radioimmunoassay to determine whether patients with marked renal insufficiency have abnormal elevations of serum myoglobin and whether there are additional patient groups seen in the Emergency Room setting that might also have elevated serum myoglobin values in the absence of acute myocar dial infarction

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Materials and methods

The method for the purification of myoglobin, immunization of rabbits and the radiolabeling of myoglobin is the same as we have described previously[1] The radioimmunoassay procedure utilized in the present study is also similar, but differs from our previously described method in the following ways In the present shortened version of the radioimmunoassay for serum myoglobin all assays were performed in triplicate in 12 × 75 mm glass tubes which were siliconized in a 1 100 silicone solution After the addition of the ^{125}I myoglobin the anti myoglobin antibody,

any other evidence of having had an acute myocardial infarct Three patients were seen in the Emergency Room with chest pain resulting from pericarditis the serum myoglobin level was normal in all three Four patients were evaluated in the Emergency Room with congestive heart failure and nonspecific chest pain each of these patients had a normal serum myoglobin value Three patients were evaluated with recent onset of atrial fibrillation each of these patients had a normal serum myoglobin determination Two patients were evaluated with diabetic acidosis one with drug overdose and one with galvanite inhalation these patients did not have clinical evidence of acute myocardial infarcts and their serum myoglobin levels were also normal Finally two patients with pancreatitis and two in shock without evidence of acute myocardial infarcts were also seen Both patients with pancreatitis had normal serum myoglobin values The two patients with shock and absent systolic pressures both had elevated serum myoglobin values initially (1 750 and 500 ng /ml respectively) in these patients the circulatory collapse was due to systemic sepsis and the patient with the highest serum myoglobin value died while the other one survived

A total of 13 blood samples were obtained from patients seen in the Emergency Room who were subsequently diagnosed as having suffered an acute myocardial infarction (Table I) The determination of myocardial infarction was made on the basis of the following (1) a typical history of prolonged and severe chest pain ordinarily associated with diaphoresis and nausea (2) classical ECG changes including the development of significant Q waves for acute transmural myocardial infarctions or ST T wave abnormalities consistent with the diagnosis of acute non transmural (subendocardial) myocardial infarction (3) classical evolution of serum creatine kinase values and (4) the development of a positive technetium 99m stannous pyrophosphate myocardial scintigram Five of these 13 patients had increased serum myoglobin values when initially seen in the Emergency Room (Table I) The mean serum myoglobin level in these five patients was 739 ng / ml with a range from 105 to 2 900 ng/ml (Fig 2) A second serum sample was obtained during the first 6 to 8 hours following admission in five of the remaining patients and in four it was elevated The mean serum myoglobin level 6 to 8 hours following hospital admission in these four patients was 401 ng /ml this represented a rise from the mean serum value of 33 5 ng /ml obtained in the Emergency Room in these same patients Two of the patients with high second serum myoglobin levels had another more prolonged episode of chest pain following admission to the hospital suggesting that they may have suffered their myocardial infarcts after admission to the hospital In the remaining four patients without elevated serum myoglobin levels in the Emergency Room two were subsequently discovered to have entered the hospital more than 24 hours after the onset of symptoms suggestive of myocardial infarction and were thus seen too late for the serum myoglobin levels to be elevated One of the remaining two patients with acute myocardial infarcts did not have a second serum sample obtained for analysis in the final patient two serum samples were obtained for serum myoglobin analysis but both values were normal

Two additional patients with recent myocardial infarcts (one 3 and one 10 days earlier) were evaluated because of recurrent chest pain In both of these patients no definite evidence of infarct extension was found and serum myoglobin values were normal in both Three patients were cardioverted for supraventricular tachyarrhythmias following admission to the hospital in each of these patients sera for myoglobin determinations were obtained 6 to 8 hours and 22 to 30 hours after cardioversion In each of these patients the serum myoglobin was normal none of the three subsequently developed evidence of having had acute myocardial infarcts (Table I)

Sera was also obtained for myoglobin measurements in 14 patients with severe renal disease (Fig 2 Table I) In those patients being dialyzed the serum samples for myoglobin and creatinine determinations were obtained immediately prior to dialysis Elevated serum myoglobin values were found in all patients with serum creatinine values above 8 mg per cent

Discussion

The data from this study demonstrate that serum myoglobin may be determined by radioimmunoassay with a 4 hour test The results obtained with the 4 hour shortened method are

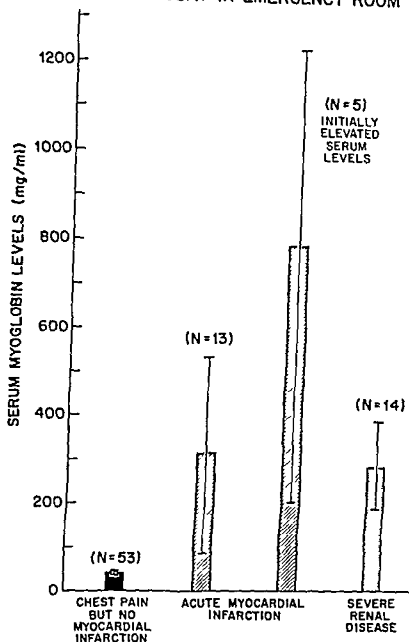


Fig 2 Serum myoglobin values in the patients evaluated in this series *Bars* represent mean values and the *cross bars connected by vertical lines* represent the standard errors

heavily (J G *see below*) and the other one (U A) who was subsequently sent home had chest pain which on clinical grounds was felt not to be due to myocardial infarction (Table I) Therefore as with the 24 hour radioimmunoassay for serum myoglobin determination any value over 85 ng /ml was considered abnormal [1] In this group of patients 10 were admitted to the coro nary care unit to rule out an acute myocardial infarct and were subsequently found not to have had one Each of these ten patients had a normal serum myoglobin value in the Emergency Room determination Twelve patients were discharged from the Emergency Room as having chest pain that did not suggest any definite significant medical illness in each of these patients the serum myoglobin level was normal in the Emer gency Room Thirteen additional patients were admitted to the hospital with a diagnosis of unstable angina pectoris, in 12 the serum myoglobin level was normal in the Emergency Room One patient in this group had an elevated serum myoglobin value This patient had been consuming large amounts of alcohol prior to admission (serum myoglobin value 180 ng /ml) None of these patients subsequently developed

Table I Cont'd

Patient no & initials	Age	Diagnosis	Serum myoglobin level (ng/ml): Emergency Room	Serum myoglobin level (ng/ml): Myoglobin determined 6-8 hours later
40 B B	3[illegible]	Mitral prolapse	[illegible]0	
41 K. C	67	Atrial fibrillation	23	
42. J W	81	Atrial fibrillation	42	
43 J D	27	Atrial fibrillation	15	
44 G H	49	Pericarditis	4[illegible]	
45 J M	53	Pericarditis	[illegible]0	
46 E H	61	Pericarditis	41	
47 J H	6[illegible]	Congestive heart failure	[illegible]0	
48 A B	64	Congestive heart failure	40	
49 J L.	8	Congestive heart failure	3	
50 S P	90	Congestive heart failure	23	
51 L. W	28	Diabetes	17	
5[illegible] C Y	[illegible]9	Diabetes	21	
53 O L.	43	Drug overdose	25	
III Patients in shock but without myocardial infarction				
1 J S	[illegible]8	Shock	500	
2. C [illegible]	51	Shock	1 50	
IV Patients electively cardioverted				
1 L. A	64	Supraventricular tachycardia	17 5	
2. R. H	51	Supraventricular tachycardia	10	
3. S C	40	Supraventricular tachycardia	65	

V Patients with renal disease

Patient	Serum creatinine (mg %)	Serum myoglobin level (ng/ml)
1 C M	16 8	850
2. G W	1[illegible]	1[illegible]5
3 J R	9 6	460
4 L S	[illegible]	1[illegible]
5 L B	1[illegible]	[illegible]0
6. G A	8.8	2[illegible]0
7 L H	10 3	3[illegible]0
8. F T	12	[illegible]0
9 P T	1 0	8
10 F G	16	1 400
11 J J	19	220
12. J J	12.3	13[illegible]
13. J P	3 6	[illegible]3
14 S A	12.1	9

similar to those found with the 24 hour incubation period we have previously described.[illegible] Thus this reduction in time required to perform the test should allow more rapid determinations of serum myoglobin by radioimmunoassay and make evaluations potentially more useful in the clinical setting.

Our attempts to utilize the shortened radioimmunoassay determination of serum myoglobin as a "triage test" for patients seen in the Emergency Room with chest pain immediately after hospital admission were only partially successful. Approximately 40 per cent of patients admitted to the hospital with severe chest pain who subsequently did have acute myocardial infarcts documented by serial enzyme and ECG testing and ^{99m}Tc PYP myocardial scintigraphy had elevated serum myoglobin levels in the Emergency Room. In contrast, another 30 per cent developed elevated serum myoglobin levels at the time of the second determinations, which were within 6 to 8 hours following being seen in the Emergency Room. In two of these patients it appeared that the actual acute myocardial infarct might have occurred following admission to the hospital since both of these patients had additional, even more prolonged episodes of chest pain associated with nausea and sweating following being admitted to the hospital. Two of the remaining four patients that did not elevate their serum myoglobin levels had their acute myocardial infarcts 24 or more hours prior to coming to the Emergency Room and in the final two patients serum myoglobin elevations did not develop even though acute myocardial infarcts were documented. In one only the initial Emergency Room serum myoglobin value was obtained for testing but in the other both an Emergency Room and a second sample were available. Presumably in the latter patient the extent of myocardial damage was small enough that serum myoglobin elevation did not occur. Thus there are definite temporal and probably quantitative limitations in the utilization of serum myoglobin determinations for establishing the diagnosis of acute myocardial infarction. If the patient presents to the hospital less than 2 or more than 24 hours after his acute myocardial infarct, then it will often be difficult to establish the presence of the infarct with a single serum myoglobin determination.[illegible] Moreover, if the myocardial infarct is quantitatively a

Table I Serum myoglobin values in patients studied

Patient no & initials	Age	Diagnosis	Serum myoglobin level (ng/ml)	
			Emergency Room	Myoglobin determined 6-8 hours later
I Patients with acute myocardial infarction				
1 E V	62	SEMI*	105	ND
2 P B	70	Inf MI*	2 900	ND
3 M B	60	Inf lat MI*	35	ND
4 E M	61	Inf MI	17 5	ND
5 R B	59	Inf MI	15	320
6 D H	76	Ant MI*	60	600
7 N C	51	Inf MI	400	ND
8 J G	44	Lat MI	33	205
9 D D	45	SEMI	130	ND
10 C R	60	Inf MI	160	ND
11 A A	58	Inf MI	45	50
12 J W	64	Inf lat MI	26	480
13 M A	68	Inf lat MI	47	ND
II Patients with chest pain but no clinical evidence of myocardial infarct				
1 G D	50	Unstable angina pectoris	25	
2 T P	44	Unstable angina pectoris	65	
3 A T	68	Unstable angina pectoris	60	
4 J M	77	Unstable angina pectoris	41	
5 I F	61	Unstable angina pectoris	31	
6 M W	50	Unstable angina pectoris	31	
7 B J	71	Unstable angina pectoris	43	
8 W B	53	Unstable angina pectoris	38	
9 E M	46	Unstable angina pectoris	28	
10 J G	53	Unstable angina pectoris	180	
11 J O	47	Unstable angina pectoris	22	
12 E O	45	Unstable angina pectoris	36	
13 B F	48	Unstable angina pectoris	4	

Abbreviations ND = not obtained SEMI = acute subendocardial myocardial infarct Inf MI = acute inferior myocardial infarct Inf lat MI = acute inferolateral myocardial infarct Ant MI = acute anterior myocardial infarct

Table I Cont'd

Patient no & initials	Age	Diagnosis	Serum myoglobin level (ng/ml)	
			Emergency Room	Myoglobin determined 6-8 hours later
14 H W	54	Chest pain of uncertain etiology but no MI	25	
15 L C	65	Chest pain of uncertain etiology but no MI	26	
16 J E	61	Chest pain of uncertain etiology but no MI	29	
17 D K	42	Chest pain of uncertain etiology but no MI	28	
18 T A	49	Chest pain	17 5	
19 B C	79	Chest pain	20	
20 A G	52	10 day old MI	29	
21 L C	56	3 day old MI	31	
22 J H	47	Insignificant chest pain	65	
23 C W	60	Insignificant chest pain	15	
24 L M	35	Insignificant chest pain	18	
25 G M	49	Insignificant chest pain	45	
26 P S	85	Insignificant chest pain	22	
27 R G	65	Insignificant chest pain	32	
28 C S	73	Insignificant chest pain	25	
29 M B	58	Insignificant chest pain	23	
30 J E	55	Insignificant chest pain	55	
31 W R	53	Insignificant chest pain	35	
32 U A	60	Insignificant chest pain	100	
33 R F	64	Insignificant chest pain	28	
34 J M	47	Insignificant chest pain	35	
35 V D	21	Pleurisy	33	
36 E B	64	Pleurisy	75	
37 H R	41	Pancreatitis	75	
38 M J	58	Pancreatitis	20	
39 W B	48	Galvanite inhalation	35	

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small one, serum myoglobin levels may not rise We have previously established in awake, unsedated experimental animals with myocardial infarcts that serum myoglobin levels begin to rise within 2 hours after left anterior descending coronary artery occlusion and generally return to normal within 24 hours after experimental infarction [3] In these same studies experimental myocardial infarcts as small as 3 gms were associated with increased serum myoglobin values and the general extent of the infarct histologically was strongly correlated with peak serum myoglobin levels [3] The present results stress the difficulty in dating the onset of acute myocardial infarction in patients and this, of course, represents a definite limitation in the utilization of the rapid determination of serum myoglobin in the recognition of acute myocardial infarcts

It also appears that shock, irrespective of its etiology, and severe renal insufficiency and in particular renal insufficiency associated with serum creatinine levels equal to or greater than 8 mg per cent are associated with elevated serum myoglobin levels In the case of circulatory collapse and shock, presumably anoxia with subsequent skeletal muscle damage is responsible for elevated serum myoglobin levels Shock is of course, known to increase certain serum enzyme values which are routinely used in the evaluation of patients for possible myocardial infarction In addition, we found one patient with none of these abnormalities who had been drinking heavily for several days prior to being seen in the Emergency Room who also had elevated serum myoglobin and creatine kinase levels Thus it may be that alcohol itself in excess is capable of producing serum myoglobin elevations as a consequence of skeletal muscle damage While we cannot prove that alcohol in excess was responsible for the serum myoglobin elevation in this patient, we feel that other investigators should be aware of this possibility so that the potential association can be further tested as other patients are evaluated Elevated serum myoglobin values in patients with severe renal disease could be the result of either decreased excretion and/or impaired metabolism of serum myoglobin as a result of the severe renal insufficiency [4, 5]

We did not find elevated serum myoglobin levels in the majority of patients with unstable angina pectoris but without enzymatic or electrocardiographic evidence of myocardial necrosis We have previously indicated that one third of patients with unstable angina pectoris have positive technetium 99m stannous pyrophosphate myocardial scintigrams and this raises the question as to whether or not these patients have had limited myocardial necrosis not detected by routine enzymatic and electrocardiographic testing [6, 7] The answer to this question is difficult to provide since temporal considerations are important, i e, the majority of these patients have had chest pain in a crescendo pattern for several days and sometimes for several weeks, thus dating the time of possible myocardial necrosis is at best difficult In the present series of 13 patients with unstable angina pectoris 11 had technetium 99m stannous pyrophosphate myocardial scintigrams and in each instance they were negative In the remaining two patients no myocardial scintigrams were obtained

Summary

The results indicate that serum myoglobin determinations may be obtained by radioimmunoassay utilizing time periods for the testing which allow more useful clinical evaluation of patients The data also demonstrate, however, that there are important temporal considerations in using serum myoglobin levels for the detection of acute myocardial infarcts and if this test is used to determine in the Emergency Room whether patients have had acute myocardial infarcts these limitations will have to be kept in mind In addition three other patient subgroups that might be expected to have elevated serum myoglobin levels by radioimmunoassay have been determined These include patients with shock (irrespective of etiology) patients with severe renal insufficiency i e, those with serum creatinine levels equal to or greater than 8 mg per cent, and possibly patients who have been on alcohol binges immediately prior to being seen in the Emergency Room

The authors wish to express their appreciation to the medical house officers and nurses working in the Emergency Room at Parkland Memorial Hospital in Dallas Texas without whose help these studies would not have been possible Our appreciation is also expressed to Mrs Belinda Lambert Ms Donna Place and Mrs Mary Rich for secretarial assistance

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Results

The effect of saralasin infusion upon mean arterial pressure heart rate and plasma catechol amine concentrations is shown in Table I After five minutes of infusion mean arterial pressure rose significantly Heart rate fell slightly but the change was not statistically significant At the end of the 30 minute saralasin infusion the mean arterial pressure was not significantly different from control for the entire group Mean arterial pressure rose 5 to 13 mm Hg in four patients remained unchanged in one and fell 9 mm Hg in one (a patient with renal artery stenosis) Neither plasma noradrenaline nor plasma adrenaline was significantly different from pre infusion levels at the end of the saralasin infusion

Table II demonstrates the effect of noradren aline infusion Mean arterial pressure rose signifi cantly and to a degree comparable to the change observed during the first five minutes of saralasin infusion Heart rate fell significantly However the change in heart rate produced by noradren aline infusion was not significantly different from that observed during the first 5 minutes of saral asin infusion The large increase in plasma norad renaline concentration observed during norad renaline infusion was 13 times that observed during the first five minutes of saralasin adminis tration A small but significant increase in plasma adrenaline concentration was observed during noradrenaline infusion

Discussion

Several of the angiotensins and structurally related peptides including those with antagonist action produced by substitution of alanine for phenylalanine in the 8 or C terminal position have been shown to release catecholamines from the adrenal medulla If this release were to have any physiologic action in man it might be expected that an increase in arterial pressure would be accompanied by an increase in heart rate since adrenaline is the predominant cate cholamine of human adrenal medulla The effect of saralasin infusion during the first five minutes of administration was to cause an increase in arterial pressure without any significant change in cardiac rate The alterations in plasma cate cholamine concentration at this point were limited to a small but significant increase in plasma noradrenaline concentration without an appreciable change in adrenaline More prolonged

Table I Effect of saralasin upon mean arterial pressure (MAP) heart rate (HR) plasma nor adrenaline (NA) and adrenaline (A) concentra tion after 5 and 30 minutes of infusion

	Control	*5 Minutes*	*30 Minutes*
MAP (mm Hg)	12[illegible] ± [illegible]	+13 ± 4	+4 ± 3
HR (beats/min)	73 ± 6	−4 ± 2	−2 ± 1
Plasma NA (pg /mL)	245 ± 34	+115 ± 28	+30 ± 23
Plasma A (pg /mL)	48 ± 5	+5 ± 2	+6 ± 4

All results are expressed as mean ± SEM Values at 5 and 30 minutes are the chang from control level.
P < 0 025
P < 0 01.

Table II Effect of noradrenaline infusion upon MAP HR plasma NA and A concentrations

	Control	*Infusion*
MAP (mm Hg)	117 ± 3	+1[illegible] ± 3
HR (beats/min)	76 ± 3	−7 ± 1
Plasma NA (pg /mL)	33[illegible] ± 37	+1[illegible]57 ± 160
Plasma A (pg /ml)	39 ± 5	+13 ± 3

Results are expressed in *Table I*
P < 0 01

infusion of saralasin was no longer associated with any significant change in concentration of either plasma catecholamine

Since the hemodynamic changes observed during the first few minutes of saralasin infusion resembled that which might be due to alpha adrenergic stimulation noradrenaline was in fused at a rate which gave an increase in mean arterial pressure similar to that which was produced by saralasin at five minutes Despite the similarity in change of arterial pressure plasma noradrenaline rose to a much greater extent than was observed during saralasin infusion Thus although the hemodynamic changes associated with the transient pressor response to saralasin bear some similarity to what might be expected from an alpha receptor antagonist the amount of circulating noradrenaline measured during saral asin infusion fails to account for the observed change in pressure when compared to infusion of noradrenaline The small increase in plasma noradrenaline detected during the initial pressure response to saralasin while having no hemody

Effect of saralasin upon plasma catecholamines in hypertensive patients

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Saralasin, (sarcosine 1, alanine 8, angiotensin II) a peptide antagonist of the vascular action of angiotensin II, reduces arterial pressure in subjects with high levels of circulating renin[1] However during the first few minutes of administration of saralasin, a pressor response is often observed regardless of the effect of more prolonged action of the drug[3,4] The transient pressor action of saralasin might be explained by the hormones of the adrenal medulla for it has been demonstrated that angiotensin and other peptides release epinephrine and norepinephrine from this organ[5] Also, it has recently been reported that a hypertensive crisis occurred during infusion of saralasin in a patient with pheochromocytoma[6] In order to assess the significance of catecholamines from the adrenal medulla in the transient pressor action of saralasin the effect of this peptide upon hemodynamics and plasma catecholamine concentration was compared to the effect of catecholamine infusion

Methods

Saralasin infusion studies were carried out in six patients Noradrenaline infusions were performed in seven patients Pheochromocytoma was excluded by determination of urine metanephrine excretion in all subjects prior to any infusion studies Infusion studies were performed during hospitalization while patients were ingesting diets containing 80 to 100 mEq sodium Diuretics were not administered Infusion studies were carried out in the supine position At one minute intervals blood pressure was measured by the Roche Arteriosonde 1216 and cardiac rate was monitored by electrocardiogram Saralasin was given intravenously at a dose of 10 μg/Kg/minute for a 30 minute period Blood samples for plasma noradrenaline and adrenaline were taken from an indwelling catheter prior to infusion after five minutes (just after the peak of the pressor response) and at the end of the infusion Noradrenaline was given at a rate of 0 1 μg/Kg/minute for 15 minutes and blood samples were obtained just before and at the end of the infusion Blood pressure measurements represent the difference between the means of 10 control determinations prior to infusion and of three determinations bracketing the time reported (i e , for five minutes the mean of blood pressure taken at 4, 5 and 6 minutes)

Plasma catecholamine concentrations were determined by a sensitive and specific radioassay[7] Forty to 100 μl aliquots of plasma in which catecholamines are preserved by the use of EGTA and glutathione are incubated with ^{3}H methyl S adenosyl methionine and catechol 0 methyl transferase to form metanephrine and normetanephrine These amines are separated by thin layer chromotography and converted to vanillin by periodate oxidation Interassay variation is less than 10 per cent and the absolute sensitivity is 1 0 picogram for either adrenaline or noradrenaline

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Case reports

Relationship between myocardial infarction and preinfarction angina*

A histopathological study of coronary arteries in two sudden death cases employing serial section

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It is necessary to clarify the initiating causes of acute myocardial infarction in order to treat or prevent this disease

So far we have studied 108 autopsied cases of acute myocardial infarction and have obtained the following results

1 Serial section of the coronary artery is needed because pathology of the lumen is extremely variable within any given 2 to 3 mm segment

2 A high incidence of thrombus formation (80 3 per cent) was observed in cases where death occurred at the acute stage

3 Occluding coronary thrombi were usually formed at the proximal part of the coronary arteries and at the sites of ruptured atheromatous plaques (incidence rate 90 8 per cent)

4 The increase of intra plaque pressure resulting from a honeycomb like accumulation of foam cells cholesterin clefts and blood infiltration from the lumen into the plaque through the injured endothelial barrier is we feel the cause of the rupture of the atheromatous plaque

5 This fracture between the lumen and the plaque might precede and be responsible for the formation of the thrombus and the onset of acute myocardial infarction

6 Fresh occluding thrombi had already been formed in patients who died within 5 to 6 hours after the onset of acute myocardial infarction

We thought it necessary to examine the patients who died suddenly after the attack of acute myocardial infarction in order to find the initiating causes of the disease

Examining coronary arteries histologically by employing serial section we have investigated the relationship between the initiation of acute myocardial infarction and preinfarction angina

Case reports

Case 1 A 70-year old retired office worker was admitted with a 5 day history of chest pain He had first noticed left precordial distress when climbing stairs and playing golf four years prior to the present illness It promptly subsided with rest but appeared occasionally during effort Thus he required no nitroglycerin However four months before admission he discontinued playing golf due to the occurrence of constant pain during this exercise Five days before admission he had a severe attack of precordial pain early in the morning which lasted for 10 minutes and which was relieved by one dose of nitroglycerin

Unfortunately the pain returned gradually and increased daily in severity and duration On the day of admission while resting in bed he suddenly developed a similar but more severe attack that lasted 1 minutes The pain was partially relieved just after 2 doses of nitroglycerin and on arrival at the CCU it had cleared completely

Physical examination The patient was well developed and nourished and had no discomfort The results of the examination were almost normal except for the presence of hypertension Blood pressure was 180/100 mm Hg and heart rate was 76 beats per minute

namic significance *per se*, may indicate a trivial release from the adrenal medulla or an alteration in function of sympathetic neurons Neuronal re uptake of noradrenaline plays an important role in terminating the action of the sympathetic neuro transmitter,[9] suggesting that changes in plasma catecholamines will reflect sympathetic neuronal activity to a very limited extent

The transient pressor effect of saralasin must be distinguished from the more prolonged eleva tion of arterial pressure that is observed when this drug is given to some hypertensive patients with low levels of circulating renin The latter action of the peptide appears best related to a partial agonist function at the site of angiotensin II vascular receptors[10] While the observations presented in this study tend to exclude release of adreno medullary catecholamines as a cause of the transient pressor action of saralasin, they do not eliminate the possibility that changes in neuro secretion by adrenergic neurons may account for this phenomenon

Summary

The effect of saralasin, a clinically employed angiotensin antagonist upon hemodynamics and plasma catecholamine concentration was com pared to the infusion of noradrenaline These studies were carried out to determine if a tran sient pressor effect frequently observed during saralasin infusion might be mediated by release of catecholamines from the adrenal medulla After five minutes of saralasin infusion, mean arterial pressure rose significantly, pulse rate fell slightly, and plasma noradrenaline increased by 115 ± 28 pg /ml Plasma adrenaline was unchanged After 30 minutes of saralasin infusion mean arterial pressure was at control levels and plasma cate cholamine concentrations were also no different from pre infusion levels Infusion of noradren aline produced a hemodynamic pattern similar to that observed during the first five minutes of saralasin infusion However, there was a thirteen fold increase of plasma noradrenaline observed when compared to the first five minutes of saral asin infusion It was concluded that the transient pressor action of saralasin could not be explained by release of catecholamines from the adrenal medulla However, the very slight increase in plasma norepinephrine observed during the first five minutes of saralasin infusion may imply altered function of sympathetic neurons

We express our thanks to the Norwich Pharmacal Company Norwich N Y for providing supplies of saralasin used in this study

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In cases where a thrombus was not detected coronary segments which showed the most severe stenosis were carefully examined by serial section All sections were stained with hematoxylin-eosin Masson s trichrome Elastica van Gieson periodic acid methenamine silver (PAM) and phosphotungstic acid hematoxylin (PTAH)

Fig 5A a section of the ri ht coronary artery 1 2 cm from the ostium shows an almost completely occluded coronary artery except for pinhole like canalization which is thought to be an old thrombus Figure 5B is a section from the left circumflex coronary artery at the branching site Here severe luminal stenosis is due to layered fibrous deposition probably formed during the frequent attacks

Fig 6A shows a section from the left anterior descending coronary artery 1 5 cm from the ostium Severe luminal stenosis is mainly attributed to atheromatous deposition Fig 6B under a hi her magnification of 6A clearly shows the thinned intimal collagen fiber and infiltration of blood elements from the lumen into the atheromatous plaque through the endothelial barrier A careful microscopic examination revealed no special changes in this arterial section which could have caused sudden death Thus further sections around the site showing the most severe stenosis were made at intervals of 100μ

Fig 6C shows a section 500μ more distal than Fig 6B In this picture rupture of the intimal collagen fiber is found The length of the fracture was 1 800μ, and the width was 800μ Discharge of the contents of the atheromatous plaque that is cholesterin clefts foam cells and ruptured intimal collagen fiber is also observed The ruptured ends of the intimal collagen fiber point toward the lumen at the fractured site These findings support the belief that the fracture occurs as a result of increasing intra plaque pres ure Fibrin has already formed and surrounds the fractured intimal collagen fiber foam cells and cholesterin clefts so the appearance of fractured intimal collegen is not due to postmortem changes

Fig 6D shows a section 00μ distal to that of Fig 6C The ruptured atheromatous plaque and the formation of fibrin i more clearly seen Fibrin and platelet aggregates adhere so strongly to the intimal collagen fiber facing the atheromatous plaque that they seem unremovable Here the intimal collagen fiber is rough and irregular so blood cells and platelets which have entered into the atheromatous plaque from the lumen are easily broken and thus platelet aggregates and fibrin are also produced

Case 2 A 69 year-old retired office worker entered the hospital with an 11 hour history of chest pain Four years prior to his present illness he experienced a severe pain in the left anterior chest admitted and diagnosed as acute anteroseptal myocardial infarction Three years after discharge he was readmitted with angina pectoris Thereafter the pain gradually increased in severity and duration and required the administration of nitroglycerin

Eleven hours before entry to the hospital he had a severe pain after dinner which subsided after two doses of nitroglycerin However as chest pain reoccurred every two hours and increased in intensity he was brought to our CCU by ambulance

Physical examination Blood pressure was 1?0 80 mm Hg heart rate wa 100 beats per minute and temperature wa 36 ° C

Laboratory findings White blood count was 10 ,00 mm

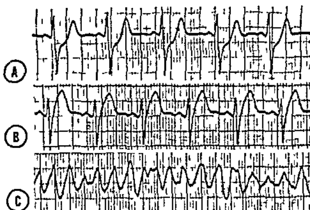


Fig 3 A through C *A* Electrocardiogram (made at 9 00 A M) on the monitor shows ST segment depression *B* ECG (made at 9 30 A M) during attack reveals ST segment elevation C Ventricular fibrillation



Fig 4 Transverse section of the heart A small transmural old scar is found at the posterior wall of the left ventricle and small old patches are localized along the endocardium of the lateral wall

and GOT was 81 units on admission GOT was 4?0 units and HBD was 890 units on the following day and LDH was 2,000 units two days after admission The electrocardiogram on admission revealed QS pattern in Leads V rS pattern in Leads $V_{5,6}$, ST segment depression in Leads II III and aV and a slight ST segment elevation in Lead aV (Fig) The electrocardiogram during attack on the following day showed Q wave and more ST segment elevation in aV Thus this patient was diagnosed as having old anteroseptal myocardial infarction and fresh high lateral infarction

Hospital course Eight days after admission the patient appeared well and had no complaints Four weeks after admission, suddenly he had severe chest pain at rest and soon after he died

Autopsy findings A large section containing both ventricles of the heart was made (Fig 8) and the location of the infarcted area was examined An old scar was found at the anteroseptal

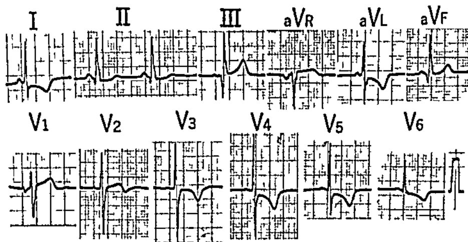


Fig 1 Electrocardiogram on admission reveals abnormal Q waves in Leads II III and aV_F and negative T waves in Leads I aV_L and V $_{6}$

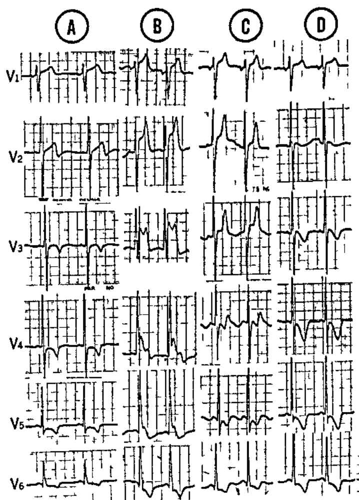


Fig 2 A through D *A* Electrocardiogram on admission shows T wave inversion in Leads V *B* ECG obtained during attack reveals ST segment elevation in Leads V *C* ECG after administration of two doses of nitroglycerin *D* ECG 18 minutes after the attack reveals deep T wave inversion in Leads V

Laboratory findings Blood sedimentation rate was 6 mm per hour and white blood count was 8 400/mm An electro cardiogram on admission revealed abnormal Q waves in Leads II III aV_F and negative T waves in Leads I aV_L and V $_{6}$ (Fig 1) This suggested old inferior myocardial infarction

Hospital course After lunch on the day of admission he developed squeezing central substernal pain radiating into the left arm This subsided only partially with two doses of nitroglycerin The electrocardiogram obtained during the attack showed ST segment elevation in Leads V_{2-5} (Fig 2*B*) Eighteen minutes after the attack the substernal pain subsided completely but the T waves were deeply inverted in Leads V_{3-6} (Fig 2*D*) compared with those on admission and these findings lasted about one week As we suspected an impending infarction we administered anticoagulant drugs and 2 tablets of isosorbite four times a day After administra tion of these drugs the patient seemed to be better but the pain occasionally occurred during effort

One month after admission at 8 07 A M while resting the patient suddenly developed a severe attack

The electrocardiogram showed deeply inverted T waves Leads in V_{2-6} The pain which was not effected by two doses of nitroglycerin persisted for 1 hour requiring the subcutaneous administration of morphine to control it Since we thought this state was an impending infarction he was again trans ferred to the CCU at 9 00 A M The electrocardiogram on the monitor showed ST segment depression (Fig 3*A*) located almost equal to Lead V_3 of a standard electrocardiogram At 9 30 A M the patient suddenly had a severe attack This time the electrocardiogram on the monitor revealed ST elevation (Fig 3*B*) Soon after ventricular fibrillation (Fig 3*C*) was recorded Cardiac massage and resuscitation were applied but unfortunately were ineffective

Autopsy findings No other probable cause of death than cardiac ischemia was found at complete autopsy

After formalin fixation the heart was cut into 1 cm thick slices in order to locate and examine the location of the infarcted area A small transmural old scar was found at the posterior wall of the left ventricle and small old patches were localized in the endocardium of the lateral wall (Fig 4)

Each main coronary artery was sectioned transversely at 3 mm throughout its entire course The calcified segments were decalcified by immersion in 5 per cent formic acid solution for 48 hours before sectioning Then they were inspected with a stereoscopic microscope and diagrammatically sketched After these initial studies each segment was then dehydrated (alcohol) cleared (xylene) embedded in paraffin and trans versely sectioned

In cases where a thrombus was not detected coronary segments which showed the most severe stenosis were carefully examined by serial section All sections were stained with hematoxylin-eosin Masson s trichrome Elastica van Gieson periodi acid methenamine silver (PAM) and phosphotungstic acid hematoxylin (PTAH)

Fig 5A a section of the ri ht coronary artery 1 2 cm from the o tium shows an almost completely occluded coronary artery except for pinhole like canalization which is thought to be an old thrombus Figure 5B is a section from the left circumflex coronary artery at the branching site Here severe luminal stenosis is due to layered fibrous deposition probably formed during the frequent attacks

Fig 6A shows a section from the left anterior descending coronary artery 1 cm from the ostium Severe luminal stenosis is mainly attributed to atheromatous deposition Fig 6B under a hi her magnification of 6A clearly shows the thinned intimal collagen fiber and infiltration of blood elements from the lumen into the atheromatous plaque through the endothelial barrier A careful microscopic examination revealed no special changes in this arterial section which could have caused sudden death Thus further sections around the site showing the most severe stenosis were made at intervals of 100μ.

Fig 6C shows a section 500μ more distal than Fig 6B In this picture rupture of the intimal collagen fiber is found The length of the fracture was 1 800μ, and the width was 800μ. Discharge of the contents of the atheromatous plaque that is cholesterin clefts foam cells and ruptured intimal collagen fiber is also observed The ruptured ends of the intimal collagen fiber point toward the lumen at the fractured site These findings support the belief that the fracture occurs as a result of increasing intra plaque pressure Fibrin has already formed and surrounds the fractured intimal collagen fiber foam cells and cholesterin clefts so the appearance of fractured intimal collegen is not due to postmortem changes

Fig 6D shows a section 100μ distal to that of Fig 6C The ruptured atheromatous plaque and the formation of fibrin is more clearly seen Fibrin and platelet aggregates adhere so strongly to the intimal collagen fiber facing the atheromatous plaque that they seem unremovable Here the initmal collagen fiber is rough and irregular so blood cells and platelets which have entered into the atheromatous plaque from the lumen are easily broken and thus platelet aggregates and fibrin are al o produced

Case 2 A 69 year old retired office worker entered the hospital with an 11 hour history of chest pain Four years prior to his present illness he experienced a severe pain in the left anterior chest admitted and diagnosed as acute anteroseptal myocardial infarction Three y ars after discharge he was readmitted with angina pectoris Thereafter the pain gradually increased in severity and duration and required the administration of nitroglycerin

Eleven hours before entry to the hospital he had a severe pain after d nner which subsided after two doses of nitroglycerin However as chest pain reoccurred every two hours and increased in intensity he was brought to our CCU by ambulance

Physical examination Blood pres ure was 1 0/80 mm Hg heart rate was 100 beats per minute and temperature was 37° C

Laboratory find ng White blood count was 10 500/mm



Fig 3 A through C A Electrocardiogram (made at 9 00 A M) on the monitor shows ST segment depression B ECG (made at 9 30 A M) during attack reveals ST segment elevation C Ventricular fibrillation



Fig 4 Transverse section of the heart A small transmural old scar is found at the posterior wall of the left ventricle and small old patches are localized along the endocardium of the lateral wall

and GOT was 81 units on admission GOT was 450 units and HBD was 890 units on the following day and LDH was 2 000 units two days after admission The electrocardiogram on admission revealed QS pattern in Leads V rS pattern in Leads V ST segment depression in Leads II III and aV and a slight ST segment elevation in Lead aV (Fig 7) The electrocardiogram during attack on the following day showed Q wave and more ST segment elevation in aV Thus this patient was diagnosed as having old anteroseptal myocardial infarction and fresh high lateral infarction

Hospital course Eight days after admission the patient appeared well and had no complaints Four weeks after admission, suddenly he had severe chest pain at rest and soon after he died

Autopsy findings A large section containing both ventricles of the heart was made (Fig 8) and the location of the infarcted area was examined An old scar was found at the anteroseptal

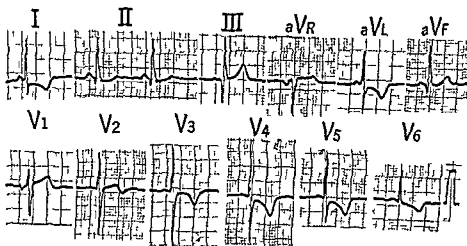


Fig 1 Electrocardiogram on admission reveals abnormal Q waves in Leads II III and aVF and negative T waves in Leads I aVL and V

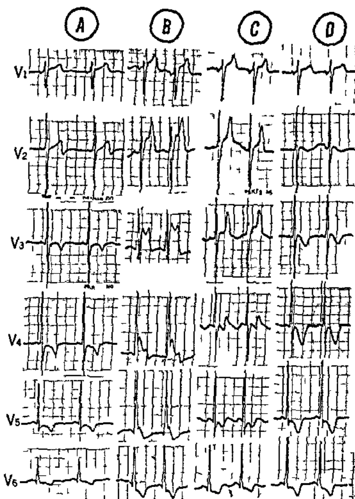


Fig 2 A through D A Electrocardiogram on admission shows T wave inversion in Leads V, *B* ECG obtained during attack reveals ST segment elevation in Leads V *C* ECG after administration of two doses of nitroglycerin *D* ECG 18 minutes after the attack reveals deep T wave inversion in Leads V

Laboratory findings Blood sedimentation rate was 6 mm per hour and white blood count was 8 400/mm An electrocardiogram on admission revealed abnormal Q waves in Leads II III aV_F and negative T waves in Leads I aV_L and V (Fig 1) This suggested old inferior myocardial infarction

Hospital course After lunch on the day of admission he developed squeezing central substernal pain radiating into the left arm This subsided only partially with two doses of nitroglycerin The electrocardiogram obtained during the attack showed ST segment elevation in Leads V (Fig 2B) Eighteen minutes after the attack the substernal pain subsided completely but the T waves were deeply inverted in Leads V_3 (Fig 2D) compared with those on admission and these findings lasted about one week As we suspected an impending infarction we administered anticoagulant drugs and 2 tablets of isosorbite four times a day After administration of these drugs the patient seemed to be better but the pain occasionally occurred during effort

One month after admission at 8 07 A M while resting the patient suddenly developed a severe attack

The electrocardiogram showed deeply inverted T waves Leads in $V_{2\ 6}$ The pain which was not effected by two doses of nitroglycerin persisted for 1 hour requiring the subcutaneous administration of morphine to control it Since we thought this state was an impending infarction he was again transferred to the CCU at 9 00 A M The electrocardiogram on the monitor showed ST segment depression (Fig 3A) located almost equal to Lead V of a standard electrocardiogram At 9 30 A M the patient suddenly had a severe attack This time the electrocardiogram on the monitor revealed ST elevation (Fig 3B) Soon after ventricular fibrillation (Fig 3C) was recorded Cardiac massage and resuscitation were applied but unfortunately were ineffective

Autopsy findings No other probable cause of death than cardiac ischemia was found at complete autopsy

After formalin fixation the heart was cut into 1 cm thick slices in order to locate and examine the location of the infarcted area A small transmural old scar was found at the posterior wall of the left ventricle and small old patches were localized in the endocardium of the lateral wall (Fig 4)

Each main coronary artery was sectioned transversely at 3 mm throughout its entire course The calcified segments were decalcified by immersion in 5 per cent formic acid solution for 48 hours before sectioning Then they were inspected with a stereoscopic microscope and diagrammatically sketched After these initial studies each segment was then dehydrated (alcohol) cleared (xylene) embedded in paraffin and transversely sectioned



Fig 6 A through D Four sections of the left anterior descending coronary artery *A* 1.5 cm from the ostium The luminal stenosis is mainly due to atheromatous deposition (Masson s trichrome stain original magnification ×25) *B* A stronger magnification of 6A Thinned intimal collagen fiber and infiltration of blood elements into the plaque are detected (Masson s trichrome stain original magnification ×50) *C* 500 μ distal Ruptured atheromatous plaque is observed here The ruptured ends of the wall of the plaque can be seen directed toward the lumen (Masson s trichrome stain original magnification ×50) *D* 1,200 μ distal Fibrin and platelet aggregates are strongly attached to the intimal collagen fiber facing the atheromatous plaque (Masson s trichrome stain original magnification ×50)

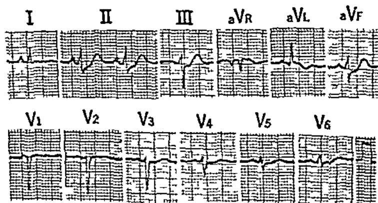


Fig 7 ECG on admission reveals QS pattern in Leads V , rS pattern in Leads V , ST segment depression in Leads II III and aV and slight ST elevation in Lead aV

of yet another coagulation factor fibrin is *formed* and it gradually accumulates to become an occluding thrombus This idea is supported by *our* results which revealed that fresh occluding thrombi were formed at the site of the ruptured atheromatous plaque in 69 of the 76 cases (90 8 per cent) Also a very small percentage of these thrombi were found to contain plaque components such as foam cells cholesterin crystals and fractured intimal collagen fiber These two find

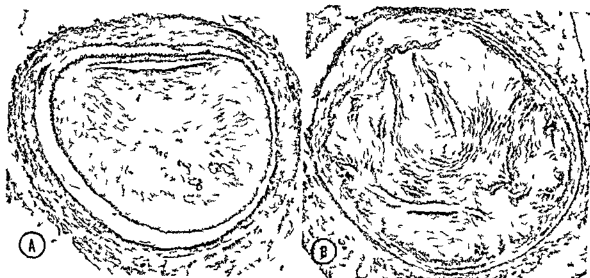


Fig 5 A and B *A* A section of the right coronary artery 1 2 cm from the ostium shows an almost completely occluded coronary artery except for pinhole like canalization (Masson s trichrome stain original magnification ×20) *B* A section from the left circumflex coronary artery at the branching site Severe luminal stenosis is due to layered fibrous deposition (Elastica van Gieson stain original magnification ×25)

wall of the left ventricle and relatively fresh granulation tissue was observed at the endocardium of the anterolateral wall The former was due to the attack which occurred 4 years before admission and the latter due to that which took place 4 weeks before death The coronary arteries were examined by the same method as in Case 1

The left anterior descending coronary artery 2 1 cm from the ostium (Fig 9*A*) shows marked stenosis due to old fibrous deposition with canalization which is thought to be an old thrombus The left circumflex coronary artery 2 4 cm from the ostium (Fig 9*B*) also shows marked stenosis with new canalization The right coronary artery 3 cm from the ostium is seen in Fig 10*A* The luminal stenosis is not so remarkable and atheromatous deposition is also slight Here there seemed to be no changes in this coronary segment which could have caused sudden death Thus further sections were made at intervals of 100μ around the site showing the plaque hemorrhage Fig 10*B* shows a section 600μ distal to that in Fig 10*A* Atheromatous deposition is larger and the infiltration of blood components is more clearly observable here Figure 10*C* is of a further 600μ distal section The atheromatous plaque is larger than in Fig 10*B* Thinned and ruptured intimal collagen fiber is found The entry of the blood elements into the atheromatous plaque is clearly observable Fibrin is also formed and surrounds the ruptured intimal collagen fiber foam cells and cholesterin clefts Discharge of the atheromatous plaque into the lumen is also seen Fig 10*D* shows a section 300μ more distal Rupture of the atheromatous plaque into the lumen is clearly demonstrable The length of the fracture was 1 200μ and the width was 700μ The ruptured ends of the wall of the plaque can be seen directed toward the lumen This suggests that the fracture occurred as a result of increasing intra plaque pressure

Discussion

A large number of reports describing the pathological events leading to sudden or unexpected cardiac death have been published[3-11] However these results do not explain the initiating cause of acute myocardial infarction As the clinical data are not so complete in cases of sudden death the relationship between the clinical course and the pathological findings is not fully elucidated

Two cases where death occurred suddenly after an attack of severe chest pain were examined and the initiating cause of acute myocardial infarction compared with clinical and pathological aspects were described

These patients had already experienced myocardial infarction before the last attack which resulted in sudden death Thus in two of the three main coronary arteries, severe luminal stenosis with old canalization was observed Ruptured atheromatous plaque had occurred in the third one by which the coronary flow was chiefly supplied The ruptured ends of the abscess wall could be seen directed toward the lumen This suggests that the increase of intra plaque pressure resulting from a honeycomb like accumulation of foam cells, cholesterin clefts and blood infiltration from the lumen to the plaque through injured endothelial barrier is the cause of the rupture of the atheromatous plaque

When this mechanical fracture has occurred platelets are exposed and become attached to the collagen Once absorbed on the collagen, the platelets swell and release the nucleotide adenosine diphosphate,[12-15] which has the property of causing further adherence of the platelets When the endothelial barrier is broken tissue thromboplastin is also released Thus under the influence

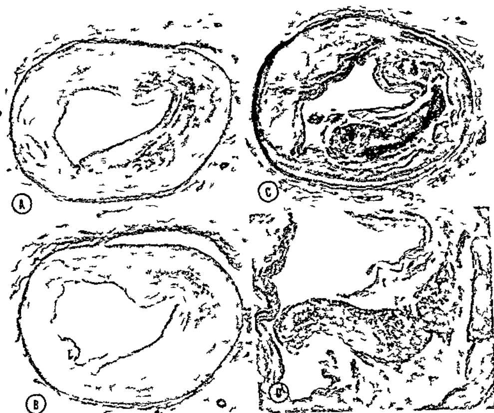


Fig 10 A through D Four sections of the right coronary artery *A* 3 cm from the ostium The luminal stenosis is not so remarkable and atheromatous deposition is also slight (Masson s trichrome stain original magnification ×20) B 600 μ distal Atheromatous deposition is larger and the infiltration of blood elements is more clearly observable here (Masson s trichrome stain original magnification ×20) *C* 1 200 μ distal Thinned and ruptured intimal collagen fiber is found The entry of blood elements into the atheromatous plaque is clearly observable (Masson s trichrome stain original magnification ×20) *D* 1 500 μ distal Rupture of the atheromatous plaque is clearly demonstrable Fibrin has already been formed The ruptured ends of the wall of the plaque can be seen directed toward the lumen (Masson s trichrome stain original magnification ×40)

attack of preinfarction angina before that of myocardial infarction The state in which the rupture of the atheromatous plaque occurs but where the occluding thrombus has not yet been formed is the state of preinfarction angina

Summary

Two patients who had previously experienced old myocardial infarction and who died suddenly after an attack of chest pain were examined and discussed In both cases two of the three main coronary arteries showed severe stenosis with canalization Ruptured atheromatous plaque was found in the unblocked coronary artery Fibrin was already formed and surrounded the fractured intimal collagen fiber foam cells and cholesterin clefts but a luminal thrombi had not yet been formed

Fresh occluding thrombi were formed at the site of the ruptured atheromatous plaque Coronary thrombi containing abscess components such as foam cells cholesterin clefts and the fractured intimal collagen fiber were found in our preliminary study

These views support the supposition that this fracture between the lumen and the plaque might precede and be responsible for the formation of the thrombus and the onset of acute myocardial infarction It was confirmed that the attack of preinfarction angina occurred at the time of the rupture of the atheromatous plaque

The rupture of the atheromatous plaque plays an important part as an initiating factor of preinfarction angina and myocardial infarction Thus it is necessary to examine coronary arteries by serial histopathological section method

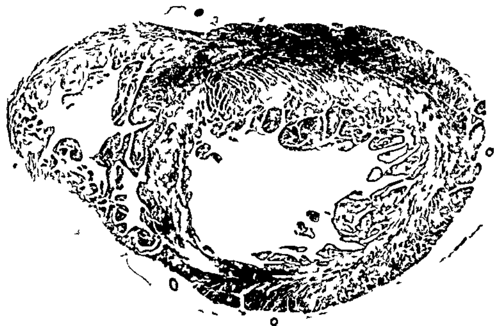


Fig 8 Large histological section containing both ventricles of the heart An old scar is found at the anteroseptal wall of the left ventricle and relatively fresh granular tissue is observed at the endocardium of the anterolateral wall (Masson s trichrome stain original magnification ×3/2)

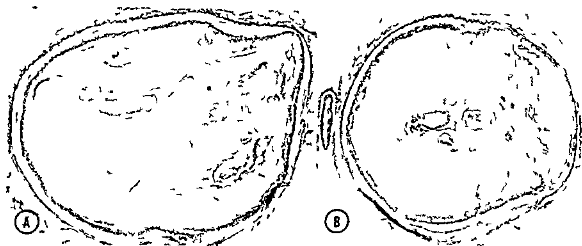


Fig 9 A and B *A* Left anterior descending coronary artery 2 1 cm from the ostium shows marked stenosis due to old fibrous deposition with canalization (Elastica van Gieson stain original magnification ×25) *B* Left circumflex coronary artery 2 4 cm from the ostium (Elastica van Gieson stain original magnification ×20)

ings have been confirmed the former by many pathologists [16,23] and the latter by Friedman [3,1]

In two cases two of the three main coronary arteries showed severe luminal stenosis The last attack is supposed to have occurred due to the rupture of the atheromatous plaque of the third main coronary artery and this proved fatal If these two main coronary arteries had been intact, fibrin would have been formed and gradually an occluding thrombus would have resulted after the rupture of the atheromatous plaque

In our histopathological study,[1] no myocardial infarction was found in those cases where the luminal stenosis of the coronary artery was supposed to have occurred gradually

We have often experienced cases of myocardial infarction where the attack had occurred suddenly Thus it requires some trigger to cause the formation of coronary thrombi and subsequent myocardial infarction

We think this initiating factor is the rupture of the atheromatous plaque This fracture between the lumen and the plaque might precede and be responsible for the thrombus and onset of acute myocardial infarction

Clinically we have sometimes encountered an

Hereditary bundle branch system defect

Survey of a family with four affected generations

Edouard Stephan M D
Beirut Lebanon

A man presumed to have died with heart block had married three wives who in four generations engendered more than 260 members Of the 209 family members examined 32 showed obvious abnormalities of the conducting system Twelve showed complete right bundle branch block (RBBB) seven exhibited incomplete RBBB six had right bundle branch block with left axis deviation four showed RBBB with right axis deviation one had left axis deviation alone and two exhibited complete heart block The pedigree pattern is compatible with the autosomal dominant mode of inheritance The onset likely congenital and the course of the disorder are discussed

It is now well established that in many instances disorders of the conducting system show a hereditary distribution Since our first two reports on a Lebanese family several examples have been described where various forms and degrees of block occurred in a parent and offspring or in two or more generations[3] An autosomal dominant defect of the conducting system has been suggested

The present family is rather unique in that it descends from a man who married three wives who engendered more than 260 members in four generations Impairment of the intraventricular conduction predominantly the right had been documented in many individuals through three and four successive generations suggesting a hereditary defect of the bundle branch system

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The proband

This 76-year-old man complained in March 1974 of dizziness Examination disclosed diabetes and evidence of right bundle branch block with left axis deviation Chest x ray films were normal During the following two years he was symptom free with no changes in the electrocardiograms In February 1976 he fainted for the first time and was then found to present an intermittent complete heart block with an atrial rate of 80 to 90 a minute a ventricular rate of 34 to 38 a minute and QRS complexes similar to those seen when the patient was in sinus rhythm A pervenous pacemaker was successfully inserted

When we realized that a half brother of the proband presented complete heart block we decided to investigate all available members of the family

Family members

The proband was the eldest son of a man who married three wives with whom he had had 16 children This man was known to suffer from heart disease with fainting attacks He died suddenly at an advanced age some 30 years ago Numerous stillbirths and early deaths occurred in the second and third generations. Some members had emigrated to Africa Therfore we could only represent in the pedigree individuals *known to be alive* in 19 6 These numbered about 260 all progeny of the common progenitor

Only two marriages of first cousins in the third and *fourth generations* were known All others were non consanguineous including the three progenitor unions

Method

Personal contact was established with all members living in Lebanon The aim of the survey was explained to all responsible persons Excellent cooperation was always obtained Several family *branches could* not be entirely covered, as approach to certain remote villages in the south of the country was not always safe during the Lebanese civil war However a total number of 209 family members could be examined

The survey included a clinical examination with a 12 lead electrocardiogram and additional right precordial leads V and V when it was necessary Due to a shortage of x ray films only 18 affected persons could have a chest roentgenogram We also had to examine 96 partners of married members of the family including the proband s wife and partners of her

The authors wish to express their thanks to Prof Akira Kajita M D for his helpful advice in the course of this study the Pathology staff for technical assistance and the Photo *section staff of the Heart Institute Japan for providing the* photographs English corrections were made by Miss Barbara Levene

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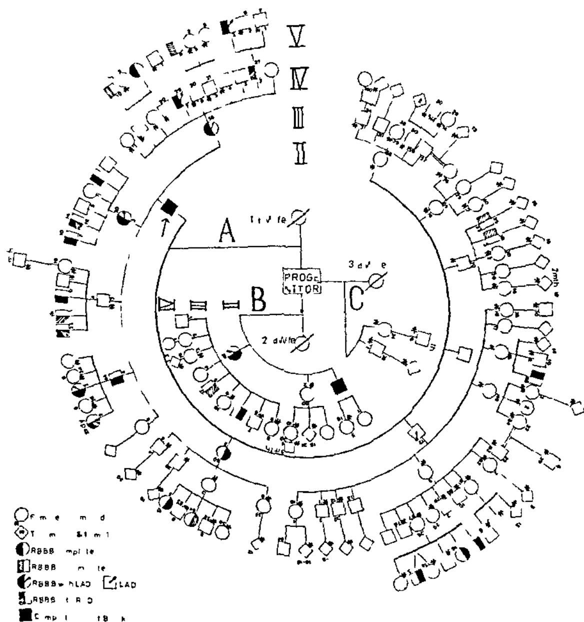


Fig 1 Pedigree of the family The three family branches issued from the unit of the progenitor with the three wives indicated by the capital letters *A* *B* and *C* the generations denoted by Roman numerals individual s serial number designated by Arabic numerals below circles and squares and age by Arabic numerals above the Proband is indicated by an arrow

affected relatives were 98 with males 54 and females 44 Incidence is thus 33 per cent with 41 per cent males and 23 per cent f males. Most cases came from the second generation and the proband progeny with a total number of 2? affected persons to ?4 non affected relatives an incidence of 48 per cent. Affected males were 15 to 11 non affected females to 13 non affected This sex discrepancy is not significant

Average age of all affected individuals is .3 years it is ?1 years for all offspring with first-degree affected relatives The ratio of affected to non affected individuals in the different age groups is represented in Fig 5

Clinical findings There were many stillbirths and early deaths in the second and third generations Two sisters A III 16 and A III 18 had had ten and seven stillbirths respectively Serology for syphilis was found negative Later A III 16 delivered nine healthy children one of whom A IV 88 presented RBBB According to the family early deaths were mainly due to common diseases of infancy and childhood and not to cardiac diseases

No special physical finding was noted There were three adult cases of ischemic heart disease Fainting only occurred in the proband case All other persons were healthy and free of

Table I Analysis of survey results

	Generation				*Total*	*Sex*		*Age*	
	2nd	*3rd*	*4th*	*5th*		*M*	*F*	*Average*	*Range*
Number in each	12	54	163	32	261	–	–	–	–
Number examined	11	42	124	32	209	109	100	16	22 days 76 yrs
Offspring with first degree affected relatives	11	22	49	16	98	54	44	21	22 days 76 yrs
Number	5	7	13	7	32	22	10	23	22 days 76 yrs
Per cent of offspring with first degree affected relatives	46	32	27	44	33	41	23		
Sex									
Male	3	5	9	5	22				
Female	2	2	4	2	10				
Type of anomaly									
RBBB									
Complete	*1*	*2*	*5*	*4*	*12*	*8*	*4*	*17*	*13 mos 60 yrs*
Incomplete	–	3	2	2	7	6	1	16	8 mos 38 yrs
With LAD	1	2	2	1	6	2	4	30	2 55 yrs
With RAD	–	–	4	–	4	3	1	16	22 days 37 yrs
LAD alone	1	–	–	–	1	1	0	72	72 yrs
Complete heart block	2	–	–	–	2	2	0	58	41 76 yrs

progeny and no conduction abnormality was found in the electrocardiograms

In the present report only well defined abnormalities of the conducting system are retained All other abnormal electrocardiographic findings were discarded

Results

Of the 209 family members examined 32 showed obvious electrocardiographic abnormalities related to the conducting system They were represented by symbols in the family pedigree (Fig 1) and are listed in Table I They included

Complete heart block Two cases the proband and his half brother B II 3

This case B II 3 a healthy man 41 years old experienced exertional dizziness 4 to 5 times during the last 3 years Repeated electrocardiograms showed complete heart block with an atrial rate of 70 to 85 a minute a ventricular rate of 35 to 38 a minute and wide QRS complexes not unlike those seen in left bundle branch block General examination routine laboratory analysis and chest x rays were normal Insertion of a pervenous pacemaker was not accepted

Right bundle branch block (RBBB) Criteria proposed by the New York Heart Association (1966) for this diagnosis were applied However in infants and young children a shorter QRS duration from 0 08 to 0 10 sec was accepted provided the right ventricular activation time was prolonged Values of at least 0 06 sec were adopted by us for the diagnosis of complete RBBB and of 0 04 to 0 06 sec for incomplete RBBB

1st degree Complete RBBB 12 cases Average age 17 years (range 1 to 60 years)

A and B indicate the family branches issued from the first and second wife Roman numerals indicate the generations Arabic numerals the individual serial number in each generation in the pedigree

2nd degree Incomplete RBBB Seven cases Average age 16 years (range 8 months to 38 years)

RBBB with left axis deviation (LAD) (frontal plane axis of the initial 0 04 portion of the QRS) Six cases Average age 30 (range 2 to 55 years) Five of these cases showed axes of −30 to −75° The sixth case A II 25 a 3 year old boy showed an axis of about −5

RBBB with right axis deviation (RAD) frontal plane axis of the initial 0 04 portion of the QRS) Four cases Average age 16 years (range 22 days to 37 years) These cases were three males A IV 2 A IV 16 and A IV 22 aged 37 14 and 14 years respectively with axes of +90 to +100° and a 22 day old baby girl A IV 27 with an axis of +150 (Fig 4)

Left axis deviation (LAD) One case a man of 72 years with an axis of −75

Figs 2 and 3 are examples of eight cases of RBBB of different ages and from each generation Fig 4 shows the electrocardiogram of the 22 day old baby girl A IV 27 who to the best of our knowledge is the youngest case of RBBB ever observed in an otherwise normal subject

There was no instance of prolongation of the PR interval Sinus bradycardia was not encountered

There were several borderline cases with an rr s or rsr s configuration in the right precordial leads without definite prolongation of the QRS (Fig 6) A few other cases showed mild degrees of left axis deviation We also encountered several instances of the S1 S2 S3 syndrome All these cases being ill defined or equivocal were not retained in the present series We also discarded four young cases with deep *q* and tall *R* waves in left precordial leads because technical facilities to rule out cardiomyopathy and congenital cardiac lesion were not available

Two first cousin marriages in the third and fourth generations resulted in 3 children with an rr s pattern out of five

Incidence and distribution The 32 affected individuals included 22 males and 10 females Offspring with first degree

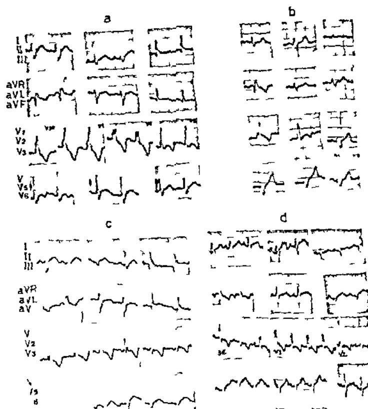


Fig 3 Four examples of RBBB in four young subjects (a) a 3-year old boy A V 8 (b) a 3-year-old girl A IV 25 (c) a 2.5-year-old girl A V 16 (d) an 8 month-old baby boy A V 10 Panels a b and c show complete RBBB d incomplete In d QRS duration is 0 08 sec right ventricular activation time 0 04 sec Axis in b is about ±0 degrees which we consider deviated to the left for that age

children A V 13 A V 16 and A V 17 after two skipped generations

The 33 per cent incidence probably is below the actual one since borderline cases have not been included However the expected ratio one to one in an inherited dominant trait is closely obtained in the generation of the proband and his progeny with 22 affected persons to 24 non affected individuals

The low female incidence though not significant may correspond to a relatively low expressivity in females. Scrutiny of the pedigree shows indeed eight instances where affected children are born to non affected parents of whom five are females A III 8 A III 16 A IV 9 A IV 77 and A III 14 and three males A II 6 A III 3 and A IV 5

Distribution according to age (Fig 5) shows a high number of affected individuals in the young age groups with six affected to four non affected individuals between 0 and 2.5 years of age There is no homogeneity in ages in the different genera

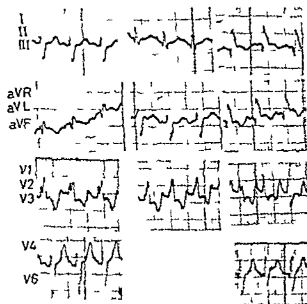


Fig 4 An instance of RBBB complete in a 22-day-old baby girl, A IV 2 QRS duration is 0 08 sec., right ventricular activation time 0 06 sec Note the marked right axis deviation of the QRS which could be normal for that age

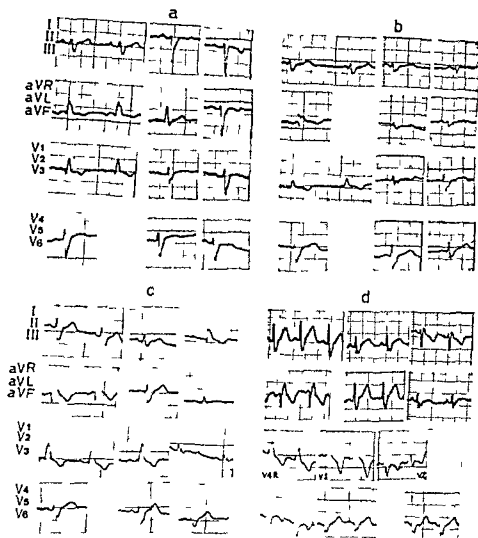


Fig 2 Four instances of RBBB from four successive generations (*a*) the proband in a period of sinus rhythm (*b*) his eldest daughter A III aged 55 (*c*) her eldest son A IV 2 aged 37 (*d*) his third son A V aged 2 Note left axis deviation in *a* *b* *d* and right deviation in *c*

symptoms related to the heart With the exception of the common progenitor no sudden death had occurred to date

Comment

Impairment of conduction in the right branch of His bundle is an almost constant feature of the affection in this family The anterior division of the left branch, as indicated by left axis deviation also seems to be involved in several cases Impairment of the posterior division is doubtful as right axis deviation in babies and young thin subjects can be normal Development of complete heart block, as it occurred in the proband case could represent total impairment of the two branches or the right branch and the two divisions of the left The same development could be incriminated in subject B II 3, though heart block in this case may already have been complete from the onset of the defect

As for borderline cases and cases with equivocal findings not included in the series some of them may correspond to minor forms of interventricular block especially when encountered in offspring of affected individuals, and more particularly in parents of affected children They will be discussed in a subsequent paper

The pedigree pattern (Fig 1), with affected individuals males and females through successive generations and in the absence of consanguinity, is compatible with the autosomal dominant mode of inheritance The trait obviously had been transmitted by the common progenitor to five children from two of his three wives and down to the fourth and fifth generation in several unbroken lines Other lineages showed skipped generations The proband s first brother A II 3 is affected with left anterior hemiblock None of his seven examined children were affected Then RBBB recurred in one grandson A IV 88 after one skipped generation and in three great grand

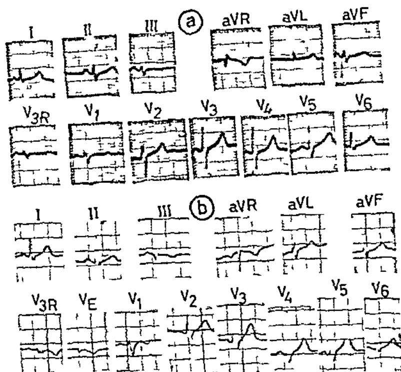


Fig 6 Minor abnormalities in two parents of affected children *a* A 26-year old woman (A IV 9) showing a double peaked r with a mild degree of left axis deviation *b* Her 31 year-old brother (A IV 5) showing an embryonic r′ In both cases the time from the onset of r to the summit of r′ is 0 05 to 0 06 sec

proband case was that of so called chronic idiopathic heart block[4] Familial survey of cases of heart block would prove to be informative and of preventive value Much also is to be known from a long follow up of this family

We wish to thank Dr V Der Kaloustian of the Department of Pediatrics American University of Beirut for his valued advice The author is grateful to his nephews, Robert Cook of the Department of Chemistry American University of Beirut and Ramzi Ashoush a medical student for their painstaking work in recording data and the pedigree

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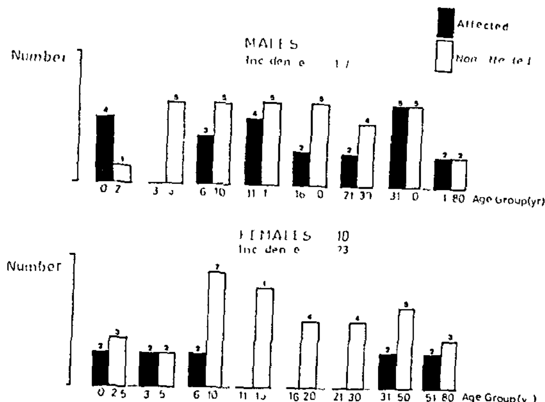


Fig 5 Age and sex distribution of affected individuals and non affected first degree relatives

tions with the exception of the fifth, where there are seven affected persons to nine non affected individuals, with an average age of two years for the affected ones Evidently, this is an early if not congenital onset

It has been customary to separate familial congenital block from block of late or adult onset, according to the age at which the disorder has been detected We now recommend that no case should be considered of late or adult onset unless documented by previous normal ECGs

Right bundle branch block associated with left anterior or posterior hemiblock is a more severe disorder than right bundle branch block alone Both probably correspond to different degrees in the expressivity of the genetic defect, since they are encountered in the same family branches in aged as well as in young persons One can assume that both types of block had been manifest at the same time, unless proved by serial electrocardiograms

At the age of 76 years, the proband advanced from right bundle branch block with left anterior hemiblock to intermittent complete heart block Progress from lesser to more advanced forms and degrees of block had been observed many times, the subject has been well reviewed [7] James[15] looks on the region of His bundle as a locus minoris resistentia, both electrophysiologically and in its tendency to undergo focal ischaemic degeneration [4] In our series the bundle branch system is already affected with one or two impaired pathways Our cases, from the beginning are in the precursor stages of heart block Theoretically, we could presume that the conducting system, in our cases, is more vulnerable to the effect of extraneous agents such as infection, stretching and especially, deficiency in blood supply These agents may, at any time provoke further damage and so precipitate heart block However there are cases of heart block from birth [4] These cases may represent a severe degree in the expressivity of the genetic defect

There was no clinical evidence to relate the conducting system disorder in this family to other familial or cardiovascular disease Two recent studies[16, 17] demonstrated in two cases of familial heart block pathology of the distal portion of His bundle and the proximal portions of the two branches In James case[16] of a 26 day old baby pathology consisted of severe caseous degeneration of these portions

Without His bundle recordings it is not possible to indicate the site of the defect whether it is at the level of His bundle or below Clinically we know that the defect had impaired the bundle branch system predominantly the right bundle branch

Many individual cases presented as bilateral bundle branch disease The evolution in the

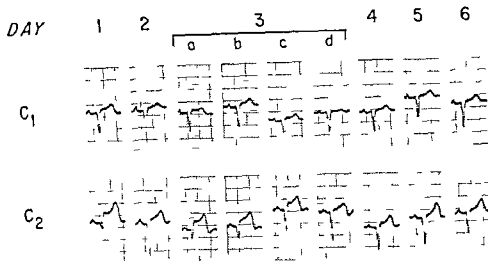


Fig 1 A 61 year old man with acute anteroseptal myocardial infarction Note ST-segment elevation on day 1 which decreased on day 2 During an episode of chest pain on day 3 marked rise of ST segments was noted (3*a*) Nitroglycerin (0 4 mg) was administered for relief Despite symptomatic response to nitrate serial maps (*a* to *c*) revealed persistent ST segment elevation which returned to the levels of day 2 one hour following the episode of chest pain No subsequent further elevations of ST segments were observed on days 4 to 6 Enzyme values were highest on day 1 and declined thereafter Abbreviations C = transverse row at the fourth intercostal space and the right sternal border (equivalent of standard V lead) C = transverse row at the fourth intercostal space and the left sternal border (equivalent of standard V lead)

of ST segment elevations 15 minutes after coronary occlusion Maroko and associates[8] utilizing unipolar epicardial electrograms from fixed sites of left ventricle in dogs have delineated the response of ST segment changes to various physiological and pharmacological manipulations aimed at altering the balance of local oxygen supply and demand These experiments revealed efficacy of certain therapeutic interventions up to 6 hours following continuous coronary occlusion Using epicardial ST segment mapping 15 minutes after coronary occlusion and estimating final extent and severity of necrosis histologically and histochemically these workers have studied the beneficial effects on ischemic myocardial injury of propranolol steroids practolol[13] reperfusion of a coronary artery after 3 hours of occlusion glucose insulin potassium regimen[5] intra aortic balloon counterpulsation[1] hyaluronidase and enriched oxygen concentrations

Good correlation of simultaneously recorded precordial and epicardial ST segment maps in the same animals and the similarity of response of both these modalities to a variety of interventions have encouraged clinical workers to apply precordial ST segment mapping in the study of patients with acute MI In both epicardial and precordial ST segment mapping the sums of all ST segment elevations recorded in millimeters (ΣST) have been taken as an index of the magnitude of the ischemic damage and the number of areas showing ST segment elevation (NST) equal and above a certain magnitude (depending on the experimental setting and the investigator) has been taken as an index of the extent of ischemic injury [3] [2] The mean ST elevation ($\overline{ST}$) the quotient of ΣST and NST has been also utilized by some workers as an index of ischemic injury of groups of animals subjected to various experimental protocols

Technique of precordial ST segment mapping

Various multielectrode ECG systems comprising 35 to 72 recording sites have been employed serially in patients in the CCU[2] A smaller number of electrodes have been used for the assessment of therapeutic interventions[22] but more data are needed to substantiate the comparability of such limited combinations of electrodes to the full multielectrode precordial map We have been employing a 49 lead precordial mapping system (1 mV = 10 mm paper speed 25 mm per second) A grid of seven transverse rows each consisting of seven recording sites is made on the patient s anterior thorax with a skin pencil

Use of precordial ST-segment mapping

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With the marked reduction of morbidity and mortality rates associated with primary dysrhythmias in patients with acute myocardial infarction (MI) clinical manifestations and prognosis has been found to be closely linked to the magnitude of myocardial ischemic damage and the resultant left ventricular dysfunction [1]

Early indicators of the extent of ischemic injury are therefore of paramount importance since their monitoring can be utilized for prognostication and for evaluation of techniques currently deemed effective in reducing the size of the ischemic damage

One of such indirect early indicators of ischemic injury is the precordial ST segment mapping Alterations of the ST segment shifts can be measured accurately and their serial recording can be utilized in the management of patients in the coronary care unit (CCU) The early appearance of changes in the electrocardiographic (ECG) ST segments in relation to the inception of coronary episode is of practical importance since interventions directed at ameliorating ischemic injury are probably more effective during the initial few hours following the onset of chest pain

The present review is based on our experience in utilizing precordial ST segment mapping in the CCU for the follow up of patients with acute MI and the evaluation of therapeutic interventions The usefulness and limitations of the technique and the significance of adherence to strict guidelines in using this modality is herein discussed

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ST segment elevation in myocardial ischemic injury

Alterations in the magnitude and distribution of ST segment shifts and changes in the direction of ST vector have been traditionally used in the clinical diagnosis of acute MI [4] Although ST segment changes have been utilized only for localization of ischemic damage an attempt for quantitation and assessment of extent of MI was made in the experiments of Prinzmetal s school, in which some correlation of the gross appearance of infarcted region and the extent of areas showing ST segment elevation at epicardial midmural, and subendocardial levels was found [5]

There is still debate as to the electrophysiological mechanism of production of ST segment elevation, although the prevailing assumption is that both true elevation of ST segment and apparent change from downward displacement of TQ segment are responsible for the ECG curves resulting from coronary occlusion A good correlation between the degree of epicardial ST-segment elevation and the reduction of myocardial blood flow drop of coronary perfusion pressure,[9] reduction of intramyocardial oxygen tension alterations in myocardial membrane action potentials,[10] and development of anaerobic metabolism[11] has been found in experiments of acute ischemic damage Excellent correlation has also been found between ST segment elevations resulting from coronary occlusion and regional functional changes of the ischemic heart in dogs [8]

More recently regional depletion of creatine phosphokinase (an excellent marker of local ischemic damage linearly correlating with segmental coronary flow) and histological and ultramicroscopic evidence of necrosis 24 hours after coronary occlusion in the dog has been found to correlate with the magnitude and extent

precordium and upper epigastrium have been utilized in the study of patients with inferior transmural MI[2] We have found this application of precordial ST segment mapping to be of no practical significance In fact often the standard 12 lead ECG showed acute current of injury in the absence of such changes in the precordial map[3]

Serial precordial ST segment maps can be of help in detecting extension of MI in the absence of evidence of extension by the standard ECG Such discrepancy between conventional ECG and precordial maps is always due to changes occurring outside the area covered by the six standard precordial leads For the diagnosis of extension clinical and biochemical parameters of change should be used along with alterations in the ST segment maps Map changes suggestive of extension of MI consist of further elevation in leads already manifesting ST elevation and/or new ST segment elevation of leads being previously isoelectric[3] Extension of MI occurred in 57 per cent of patients with anterior MI in one study We have also found a 48 per cent extension rate in a similar group of patients[3] From the 20 patients who suffered an extension in these two studies seven patients had more than one extension[3 2] This observation coupled with the timing of extension of MI (5 8 and 2 4 days after admission) suggests that interventions aimed at reducing the severity of ischemic damage in the early phase of admission should be probably followed by therapeutic manipulations directed at preventing extension of injury in the subacute phase

The sensitivity of precordial ST segment maps in diagnosing MI s undetected by conventional ECG has not been studied heretofore Clinical applications of the technique has been carried out in patients selected on the basis of evidence of current of injury in the standard ECG [3 2] Two patients one with lateral and one with inferior transmural MI s have been reported to have shown changes in the precordial maps in the presence of nondiagnostic 12 lead ECG We have diagnosed the true posterior and high anterior components of a lateral MI (diagnosed by standard ECG) using maps Leads from the posterior thorax were used to diagnose true posterior MI

Precordial ST segment maps have been utilized in clinical studies for the evaluation of therapeutic interventions Hyaluronidase[4] nitroglycerin practolol[5] propranolol[6] and intra aortic balloon counterpulsation have been found to reduce ΣST and NST in patients with acute anterior MI We have also found that oxygen administration to patients with MI resulted in reduction of ΣST and NST This change was reversed when patients returned to ambient air breathing Combinations of interventions have also been tried[9] In general such clinical applications of precordial ST segment maps consist of either serial mapping of a treated and a matched control group or serial mapping of the experimental group which is used as its own control[5 4] Since alterations of ΣST and NST can occur independent of application of therapeutic interventions the importance of continually monitoring the patients clinical status during the study period cannot be overemphasized[3 9]

Limitations of precordial ST segment mapping

Patients with bundle branch block or implanted pacemakers cannot be studied with precordial ST segment maps since alterations of ST segments secondary to conduction abnormalities affect markedly the magnitude of ST segments[3] In the presence of pericarditis also serial precordial ST segment mapping should be terminated since the technique does not yield any useful information with such complication occurring[3] When a clear cut history of onset of chest pain is lacking meaningful precordial ST segment mapping cannot be carried out such absence of information hampers correlation of precordial maps with other data and results in mixing patients with infarct of different age The technique can only be applied to patients with anterior and lateral transmural MI Inferior transmural MI or nontransmural MI cannot be mapped[3] Since the magnitude of ST segment alterations depends not only on the underlying epicardial ST segment changes but also on the electrical resistance of tissues distance of the recording electrodes from the ischemic epicardial region position of the heart in the chest[1] projection of the infarcted area onto the anterior thoracic wall and unpredictability of boundaries of ischemic damage[3 21] ΣST and NST cannot be taken as quantitative measurements of underlying ischemically damaged muscle It is probably relevant that precordial ST segment maps done in normal male volunteers produced higher ΣST

and it is kept for the total hospitalization of the patients[1] The first row (A) is made at the level of *second intercostal space The second row (B)* is put at the third intercostal space Rows C to G are placed at distances equal to the distance between rows A and B Recording sites form seven vertical columns (1 to 7) Column 1 is positioned at the right sternal border and column 2 at the left sternal border Column 5 is placed at *the anterior* axillary line with columns 3 and 4 spaced evenly between columns 2 and 5 Columns 6 and 7 are made at the mid and posterior axillary lines, respectively Recordings are made via the V lead of an ECG machine utilizing a Welsh self retaining ECG electrode (HP Part No 9301 0122) with a contact diameter of 15 mm and *applying HP Redux ECG* creme Five beats or more from ECG tracings with stable baseline (no more than 1 0 mm baseline shift *in five successive* beats) are used in the measurement of ST deviations ST segment deviations are measured in millimeters to the nearest 0 5 mm , 0 06 sec after the nadir of S wave using the TP segment as an isoelectric line except in cases of tachycardia when the PR segment is used instead[3] This portion of ST segment has been found to be devoid of influences from atrial repolarization or QRS and T wave alterations[1] Meticulous adherence to the recording techniques should be exercised We have found that varying the location of *the V' electrode by 1 cm could alter the magni*tude of ST segment elevation by as much as 1 5 mm[3] Except for the initial study, mapping is not carried out during chest pain episodes[3, 10] since recordings during post MI angina often produce marked transient ST segment alterations (Fig 1) Simultaneously with the precordial ST segment *maps* blood *pressure* heart *rate,* details of patient s symptomatology data from physical examination and informations on applied therapy should be recorded and timed Data from serial sampling of enzymes or recording of other parameters *of extent of injury should be timed for* proper correlation with serial ST segment maps

Reproducibility and stability of the technique of ST segment mapping

Epicardial ST segment *maps done in dogs* subjected to two successive 20 minute coronary *occlusions* 1 hour apart (for full recovery between occlusions) produced unchanged ΣST and NST[8] Also interobserver variations in the values of ΣST in precordial tracings from dogs was within 3 per cent and for NST was zero Precordial maps done 15 minutes apart in clinically stable patients produced stable values for ΣST and NST[2] *Regarding the stability of precordial* ST segment maps over time data are available In a group of 28 consecutive patients with anterior MI studied 6 ± 1 hours after onset of chest pain with two ST segment maps 1 hour apart stable ΣST and NST was found, except when change in the clinical status took place in the interim[3] In other clinical *trials in which interventions were applied the* control, untreated group showed stable ST segment maps over a 2 hour period and the treated group maintained stable precordial maps in the 1 hour preceding the onset of interventions[2] It cannot be overemphasized that reproducibility and stability over time of the technique *is mandatory for its utilization in the assessment* of currently proposed therapeutic interventions[3]

Clinical application of precordial ST segment mapping

Precordial maps have been utilized by several workers in following patients with anterior and lateral MI[3 0 1] A pattern of maximal ST segment elevations surrounded by smaller degrees of ST *elevation has been* unanimously found[3 0 1] Variability of the gradual reduc*tion of ΣST and NST has been noted* with maximal change occurring in the early phase of MI[9] A 29 to 31 per cent decline in the ΣST within the initial 24 hours has been noted[3] Chest pain (Fig 1), ventricular fibrillation and reduction of arte*rial pressure have been found* to enhance ST segment elevation[2, 1] Pericarditis which produces stable high ST segment elevations has been found to invalidate the technique completely and is found quite often if sought for intensively[3]

Some workers have utilized precordial ST *segment* depression *maps* in the study of anterior nontransmural MI[9] Since there are no data presently available correlating ST segment depression with other markers of regional ischemic damage or necrosis further substantiation of the validity of precordial ST segment depression maps is needed

Precordial mapping of ST segment depressions noted in the upper precordium *in conjunction to* ST segment elevations recorded from lower

precordium and upper epigastrium have been utilized in the study of patients with inferior transmural MI.[3, 22] We have found this application of precordial ST segment mapping to be of no practical significance. In fact, often the standard 12 lead ECG showed acute current of injury in the absence of such changes in the precordial map.[3]

Serial precordial ST segment maps can be of help in detecting extension of MI in the absence of evidence of extension by the standard ECG. Such discrepancy between conventional ECG and precordial maps is always due to changes occurring outside the area covered by the six standard precordial leads.[3, 20] For the diagnosis of extension, clinical and biochemical parameters of change should be used along with alterations in the ST segment maps.[3] Map changes suggestive of extension of MI consist of further elevation in leads already manifesting ST elevation and/or new ST segment elevation of leads being previously isoelectric.[3, 7] Extension of MI occurred in 57 per cent of patients with anterior MI in one study. We have also found a 48 per cent extension rate in a similar group of patients. From the 20 patients who suffered an extension in these two studies, seven patients had more than one extension.[3] This observation, coupled with the timing of extension of MI (5.8 and 2.4 days after admission), suggests that interventions aimed at reducing the severity of ischemic damage in the early phase of admission should be probably followed by therapeutic manipulations directed at preventing extension of injury in the subacute phase.

The sensitivity of precordial ST segment maps in diagnosing MIs undetected by conventional ECG has not been studied heretofore. Clinical applications of the technique has been carried out in patients selected on the basis of evidence of current of injury in the standard ECG.[2, 20] Two patients, one with lateral and one with inferior transmural MIs, have been reported to have shown changes in the precordial maps in the presence of nondiagnostic 12 lead ECG.[2] We have diagnosed the true posterior and high anterior components of a lateral MI (diagnosed by standard ECG) using maps. Leads from the posterior thorax were used to diagnose true posterior MI.[3]

Precordial ST segment maps have been utilized in clinical studies for the evaluation of therapeutic interventions. Hyaluronidase,[4] nitroglycerin,[?] practolol,[5] propranolol,[6] and intra-aortic balloon counterpulsation[27] have been found to reduce ΣST and NST in patients with acute anterior MI. We have also found that oxygen administration[8] to patients with MI resulted in reduction of ΣST and NST. This change was reversed when patients returned to ambient air breathing. Combinations of interventions have also been tried.[2] In general, such clinical applications of precordial ST segment maps consist of either serial mapping of a treated and a matched control group[??, 24] or serial mapping of the experimental group which is used as its own control.[5, 8] Since alterations of ΣST and NST can occur independent of application of therapeutic interventions, the importance of continually monitoring the patients' clinical status during the study period cannot be overemphasized.[3]

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than in the ones recorded from female subjects, the difference was attributed to dissimilar chest characteristics of the two groups [9] It should be also emphasized that precordial ST segment maps reflect the epicardial component of MI, whereas prognosis and clinical status are influenced by the total size of the MI, which includes a substantially broader subendocardial component [3,5] Despite these limitations and the lack of clinical studies correlating ST segment maps with other direct indicators of ischemic damage, this technique is useful in the monitoring of *directional* changes of ischemic injury as a result of natural evolution or application of therapeutic interventions It is hoped that continuing clinical research in this exciting area will contribute to the development of a new approach in confronting the complications of power failure in the early setting of acute MI

Summary

Serial precordial ST segment ECG mapping with a grid consisting of 49 recording marks made on the anterior thorax of patients with acute anterior transmural myocardial infarction has been applied in the study of usefulness of this technique It has been found that a pattern of variable devolution of the magnitude of ST segment elevations is seen in uncomplicated myocardial infarction Extension of the infarct has been characterized by re elevation of ST segments Beneficial therapeutic interventions have resulted in reduction of the magnitude of ST segment elevation However the technique cannot be applied in patients with inferior transmural myocardial infarction or in patients with functioning pacemakers, bundle branch blocks or pericarditis The significance of adherence to strict guidelines in performing ST segment mapping and the analysis of mapping data in the light of the total clinical picture at the time of recordings is emphasized

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Concepts and applications of treadmill exercise testing and the exercise electrocardiogram

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Stress electrocardiography has become an integral tool in the clinical evaluation and management of patients with suspected or known cardiovascular disease It is also commonly used as a *screening procedure for normal subjects thought to be at risk of ischemic heart disease* Exercise testing with electrocardiographic monitoring was first proposed by Goldhammer and Scherf[1] in 1932 as an aid in the diagnosis of ischemic heart disease Master [3] later developed and modified his two step test to achieve this same goal However subsequent investigators[4-6] demonstrated that the two step test lacked sufficient *sensitivity* and graded exercise testing came into* common use Other forms of stress electrocardiography have been evaluated such as induced hypoxia [7] isometric exercise,[8] and atrial pacing [9] These methods have not gained wide acceptance due to difficulties in performance and standardization as well as a lack of sensitivity and specificity * Multistage exercise protocols have been *developed for stress electrocardiography using* either a motor driven treadmill or an electrically braked bicycle ergometer The remainder of this review will be limited to treadmill exercise testing since this is the most prevalent method of stress testing in use today

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*Sensitivity refers to the per cent of patients with coronary artery disease who manifest a positive stress ECG Specificity refers to the per cent of patients who are free of coronary artery disease who have a negative stress ECG

Pathophysiologic basis of exercise testing

Even with advanced *coronary artery disease* the myocardial oxygen *supply may not be* reduced significantly at rest to cause myocardial ischemia The basic premise of exercise testing is to increase the myocardial oxygen requirements to unmask a reduced relatively fixed coronary blood flow The resultant myocardial ischemia may then be detected through *electrocardiographic abnormalities usually in the form of* ST segment changes Controversy still exists as to what degree of coronary arterial stenosis constitutes a significant obstructive lesion An 85 per cent stenosis is required to decrease resting coronary blood flow in the experimental animal [10] *It is generally accepted that an obstruction of at least* 50 per cent of the arterial lumen is necessary to cause a coronary flow restriction during exercise induced stress [10,11] Exercise leads to an increase in myocardial oxygen consumption through its augmentation of heart rate intramyocardial tension and the velocity of *contraction of the myocardium* [1,13] *Increases in heart rate are* associated with a fairly linear increase in myocardial oxygen consumption[14,15] and the exercise heart *rate provides one easily* monitored parameter of myocardial oxygen requirements By additionally monitoring the blood pressure during *exercise the simple product of heart rate* and systolic blood pressure can be calculated and this appears to be a practical index of myocardial oxygen requirements for the clinical laboratory [13,14,16]

Methodology

Multistage exercise protocol Multistage treadmill exercise protocols provide for progressive increments in work load following an initial low work load period to allow proper warm up of the patient An example is the modified Balke protocol currently used in our laboratories (Table I) Interval increases in work load can be accompanied by changes in speed and/or grade (incline) At least three minute intervals are preferable so that steady state blood pressure and heart rate responses can be achieved The optimal protocol should be designed to allow the patient to exercise at least three minutes without limiting symptoms to assure a functional evaluation of the patient Protocols calling for speeds above 4 0 m p h require patients of shorter stature to run or jog to keep pace and this often leads to an unacceptable deterioration of the ECG signal Irrespective of which exercise protocol is routinely utilized the treadmill speed or grade for any given stage may have to be reduced by the monitoring physician to accommodate the older patients or patients with moderately severe angina The Bruce protocol is commonly used in part because of the availability of physiologic data which allow for an estimation of the patient s functional aerobic impairment Using the patient s duration of exercise and a nomogram one can estimate what per cent of his predicted maximal oxygen consumption the patient was able to achieve A failure of the patient to achieve a predicted level of exercise may be the result of cardiovascular impairment However a potential shortcoming of this method of assessing a patient s functional impairment is that it depends on the patient exercising to his self determined maximal capacity Patient motivation may be an important limiting factor as can be the physician s estimation of the patient s daily activity status (sedentary normally active etc)

Electrode placement and skin preparation The quality of the recorded ECG signal is the single most important technical aspect of exercise electrocardiography The proper choice of electrodes and skin preparation at the site of electrode placement insure the greatest likelihood of obtaining high quality ECG records with submaximal and maximal exercise testing In at least 10 per cent of patients with exercise induced ischemia the ST segment abnormalities will appear

Table I Graded multistage exercise protocol

Exercise stage	*Time (min)*	*Treadmill speed (miles/hour)*	*Treadmill grade (%)*
I	3	2 0	3
II	3	3 3	6
III	3	3 3	9
IV	3	3 3	12
V	3	3 3	15
VI	3	3 3	18
VII	3	3 3	21

only during exercise[3] and excessive noise motion artifact or baseline drift may obscure the diagnostic ST segment changes Potentially dangerous exercise induced arrhythmias may also be missed

Adequate skin preparation consists of first cleansing the sites of electrode application with ethyl alcohol followed by removal of the superficial epidermal layer with a dental burr mounted on a high speed drill or by light abrasion with fine grain sandpaper Too vigorous debridement should be avoided to prevent edema formation and an increase in electrical resistance at the electrode-skin interface Once the superficial epidermal layer is loosened it should be washed away by light cleansing with acetone

The optimal electrode is one of silver-silver chloride composition The electrode should be one centimeter in diameter or less and encased in a lightweight plastic well which is two or three millimeters deep This design avoids electrode contact with the skin and reduces baseline drift

In female subjects the exercise ECG should be carried out with the patient wearing an undergarment to support the breasts This will prevent the motion artifact caused by movement of the chest electrode by the breasts during exercise

Lead systems The monitoring lead systems which will detect ischemic ST segment responses with optimal accuracy and sensitivity have not yet been clearly defined The most commonly used lead systems are the bipolar V_5 leads denoted CC_5 (right V_5 to left V_5) CB_5 (tip of right scapula to V_5) or CM_5 (manubrium to V_5) Although the CB_5 has the theoretical advantage of being parallel to the major ST segment vector shift during exercise it has the practical disadvantage of excessive motion artifact and skeletal muscle noise Blackburn reported CM_5 to be slightly

Table II Age predicted target heart rates*

Age (years)	*90% predicted maximal (beats/min)*	*Maximal (beats/min)*
20	178	200
25	175	196
30	170	191
35	165	187
40	160	180
45	155	176
50	150	170
55	145	167
60	140	160
65	135	156

Adapted from Blackburn H W Developments in Exercise Electrocardiography Proceedings of the 5th Annual Meeting of the Medical Section of the American Life Convention 1969

more sensitive in detecting ST segment shifts However the CM lead, because of its semi vertical orientation may increase the incidence of false positive tests

In our laboratory a modified CC_5 lead is used for the X axis recording The RV_5 position is standard while the exploring electrode (left V_5) is placed somewhere between the V_4 and V_6 positions in the fifth or sixth interspaces The placement is chosen to yield a similar large R small s (Rs) complex in all patients This approach eliminates the problems of optimal detection of ST segment shifts caused by precordial patterns of clockwise or counterclockwise rotation A higher interspace is selected in patients with marked left axis deviation or an electrically horizontal heart on their resting ECG Similarly a lower interspace is selected in those patients with an electrically vertical mean QRS axis The technician can be trained to select the optimal placement of the exploring bipolar electrode by analysis of the 12 lead ECG in the majority of patients

The advantages of simultaneous recordings from multiple lead placements during exercise testing is still under active investigation[17] To date the increase in diagnostic yield one can expect from the use of multiple leads is unclear The authors are unaware of a completed study which has compared multiple lead placements to a single modified V_5 placement such as is used in our laboratories If an increased sensitivity for detecting myocardial ischemia is demonstrated using multiple leads their widespread clinical application will be warranted, assuming specificity is not compromised to a degree which will nullify the value of the increase in yield At present the technical problems inherent in orthogonal and multi lead systems make them less desirable from a practical standpoint in routine clinical treadmill testing

Endpoints for multistage exercise testing The endpoint chosen for terminating a multistage treadmill exercise test may affect the diagnostic sensitivity of the examination In order to assure the greatest possible diagnostic yield the patient should be stressed to a near maximal level This will also provide an adequate assessment of the patient's cardiovascular function The exercise heart rate is an easily measured index of myocardial oxygen consumption and predicted near maximal heart rates are generally accepted as suitable endpoints[11,13,1] Table II shows near maximal target heart rates for various age groups of normal subjects Once the patient attains the predicted heart rate without symptoms the test can then be terminated at the discretion of the monitoring physician When an assessment of cardiovascular function is desired some physicians favor a self determined maximal effort endpoint When using this endpoint the monitoring physician must always assess the subjective and motivational aspects of the patient's performance to judge whether it was truly a symptom limiting maximal effort[1] In the authors opinions the physician should never insist that the patient reach a predicted heart rate or continue to a maximal effort if he is experiencing symptoms of an intensity which would prompt him to cease his daily activities When testing patients with exertional angina to determine their exercise tolerance the onset of chest pain may be the desired endpoint If the test is also being carried out for diagnostic purposes the time of onset of chest pain should be noted but if diagnostic ST changes are not apparent the physician should cautiously urge the patient to continue until the intensity of his angina reaches that experienced in his day to day activities This approach may increase the yield of positive ST segment responses by as much as 15 per cent without placing the patients at added risk The first onset of chest pain has proved to be a more practical and reproducible endpoint for serial testing in our experience If variations in time of onset of chest pain are noted with serial testing it can usually be shown that the product of the

t rate and systolic pressure has remained the e [5] In patients with known coronary disease who do not experience angina during treadmill testing it is generally recommended that a ceiling of 90 per cent of predicted maximal heart rate be used [5]

Using the above guidelines functional capacity testing of patients with coronary artery disease can be very helpful in defining their exercise tolerance levels Exercise prescriptions and permissible work activities can then be recommended Serial tests can also be used to assess any positive or negative effects of medical or surgical interventions

As an epidemiological tool for screening asymptomatic subjects maximal treadmill exercise testing imposes a significantly greater cardiovascular work load than submaximal exercise and can be expected to yield a greater incidence of positive ST segment responses In this setting the physician must be aware of the significant number of false positive responses which will occur

ECG and hemodynamic monitoring Monitoring techniques vary among different laboratories However there are basic requirements to insure patient safety and the capability of recording data of diagnostic value A continuous oscilloscopic display of the exercise ECG and capability for intermittent ECG write outs are mandatory to enable proper analysis of arrhythmias and ST segment changes The ability to *monitor accurately* cuff arterial pressure in the upper extremity during exercise is also necessary In the patient with known or suspected heart disease the exercise ECG and blood pressure should be recorded at minute intervals during exercise and through at least six minutes postexercise These parameters should always be recorded whenever symptoms physical signs or arrhythmias develop Emergency equipment for cardiopulmonary resuscitation defibrillation and drug administration should be readily available The presence of a physician knowledgeable in exercise testing is mandatory during the performance of a treadmill exercise test

Safety and contraindications

Statistics reported by many exercise testing facilities document the extremely low risk of morbidity and mortality associated with multistage treadmill exercise testing Morbidity-mortality data collected by Rochmis and Blackburn[3] in 1971 using the multicenter questionnaire technique encompassing over 170 000 exercise electrocardiographic tests (treadmill bicycle ergometry and Master s two step) showed only 16 deaths and 40 patients requiring hospitalization for nonfatal complications Thus the reported mortality and morbidity of exercise testing is very low It should be noted that these risks prevail in testing facilities where exercise is carried out and supervised by experienced personnel All patients undergoing exercise testing should have at least a basic cardiovascular history and a physical examination prior to exercise A current 12 lead ECG is mandatory to rule out unsuspected myocardial infarction This initial patient-physician contact serves to establish rapport and allows the physician an opportunity to explain the goals procedures and safety of the planned exercise test to the patient Some authorities recommend obtaining a written informed consent [3] while other exercise laboratories rely on verbal communication with the patient to establish implied consent Exercise testing has enjoyed a relative freedom from associated litigation [3]

The contraindications for exercise testing are listed in Table III As noted most of these are only relative contraindications and testing may be carried out for the elucidation of particular clinical problems using reduced work loads initially and more frequent assessments of the monitored parameters

Indications for termination of an exercise test short of the target heart rate or limiting symptoms are listed in Table IV Some laboratories use *paired* ventricular premature complexes as an indication to terminate testing We have used the criterion of three consecutive ventricular premature complexes rather than two and have observed no complications arising from this practice A declining heart rate or a sustained and reproducible drop in blood pressure in the face of progressive work loads suggests multivessel coronary disease with severe ischemia or cardiac failure [3] A decline in these parameters is occasionally observed during the first stage of exercise in patients who are initially quite anxious and under these conditions there is no need to terminate the test Symptoms or signs of progressive heart failure or cerebrovascular insufficiency are also indications to terminate the test Excessive ST segment depression is a relative indication for

Table III Contraindications to exercise testing

Absolute	Relative
Recent myocardial infarction or *ischemic event* (known or suspected)	Accelerating angina pectoris without rest pain
Unstable angina pectoris with recent episodes of rest pain	*Severe valvular disease* with history of syncope or failure
Overt congestive heart failure	Serious ventricular or supraventricular *arrhythmia at rest* or during previous exercise testing
Serious ventricular arrhythmia at rest refractory to therapy	Recent thrombophlebitis and/or embolism
	Active chronic (uncontrolled) systemic processes including hypertension thyroid renal or hepatic disease
	Acute non cardiac illnesses
	Inordinate anxiety

Table IV Indications for early termination of an exercise test

Absolute indications

1. Declining blood pressure or heart rate response to *progressive work loads*
2. Ventricular tachycardia (3 or more consecutive ventricular premature complexes)
3. Ataxia or gross gait disturbances
4. Vertigo or visual disturbances
5. Appearance of advanced degrees of heart block
6. Cyanosis or pallor

Relative indications

1. Frequent ventricular premature beats including bigeminy and multifocal ectopy
2. Excessive *ST segment depression*
3. Chest pain (see text for description)
4. Inordinate anxiety
5. Dizziness or unsteadiness of gait
6. Supraventricular arrhythmia with rapid ventricular response
7. Limiting dyspnea or fatigue

terminating exercise Although multiple factors *affect the degree of ST depression* there is a fair correlation with the severity of coronary artery disease and presumably with the extent of myocardial ischemia [illegible] Discontinuing exercise when the ST response is definitely positive may be appropriate for diagnostic testing although in doing so the monitoring physician may be deprived of additional information such as the later reproduction of classical angina which would be supportive in the diagnosis of ischemic heart disease The authors feel that irrespective of the primary purpose of the exercise test the physician should always attempt to define the patient's exercise tolerance or functional capacity, and thus the patient's limiting signs or symptoms (such as a declining blood pressure or the onset of angina) should be defined within the constraints previously outlined If marked degrees of ST segment depression occur then the monitoring physician must make a decision concerning termination of the test based on the clinical circumstances of the individual patient

ECG criteria for an abnormal exercise electrocardiogram

The establishment of criteria for a positive or ischemic exercise ECG has been the subject of much investigation However, a uniform acceptance *of specific criteria still does not exist* Master's ECG criteria for a positive single stage exercise test was 0.5 mm of horizontal or down sloping ST segment depression in the postexercise recording Later studies using coronary cineartenographic correlations established the criteria for a positive ST response as 1.0 mm or greater of horizontal ST depression which persists for at least 0.08 sec [illegible] These criteria were found to reduce *the relatively high number of false* positive responses observed when only 0.5 mm of *ST depression was used as a criterion* If one selects 2.0 mm of ST depression to further reduce the incidence of false positive responses the specificity is further enhanced However, the sensitivity of the test in patients with coronary artery disease then becomes unacceptably low [illegible] The advent of multistage treadmill exercise testing and ECG recordings during strenuous exercise has brought about a reappraisal of the previously used postexercise *ST segment criteria* It has been suggested that the analysis of the ST *segment during exercise* should include consideration of slowly upsloping ST depression [illegible] Since graded exercise testing with ECG recordings during exercise results in much faster heart rates and more abbreviated ST segments Bruce and Hornsten [illegible] have recommended that the point at which ST depression is measured be shortened *from 0.08 to 0.06 sec after* the J point

The criteria currently used in our exercise

laboratories for a positive postexercise (beyond one minute recovery) ST response are 1.0 mm or greater of horizontal or downsloping ST depression. When interpreting the ST segment response during exercise or in the immediate recovery period, we feel these criteria are too rigid and slow upsloping ST criteria can be utilized without compromising the specificity of the test. Computer averaging techniques are used in our laboratories to measure the ST depression and slope, but reliable measurements can be made with direct write outs of the ECG at 50 mm./sec. assuming high quality ECG recordings are obtained. Several investigators have reported a reduced specificity using slow upsloping ST segment criteria, but these results may have been influenced by their application of the criteria to the postexercise ST segment. Preliminary evidence has been presented to suggest that the type of V monitoring lead system used may also influence the results when slow upsloping ST segment criteria are used. The findings of two recent studies evaluating the use of slow upsloping ST segment criteria during exercise (1.5 mm. or > of ST depression at 80 msec. beyond the J junction) seem to support the use of these criteria in the diagnostic exercise ECG.

The appearance of isolated T wave inversion during or after exercise is of no diagnostic significance as it is commonly seen in patients without disease. Robb and Marks found no increased long term mortality associated with isolated T wave negativity.

Exercise records which have normally upsloping ST segments during exercise but demonstrate horizontal or downsloping ST depression in the late recovery period merit special attention. Using computer analysis techniques for precise ST segment measurements during exercise, we have found that the majority of coronary heart disease patients who demonstrate unequivocally abnormal ST depression late postexercise will have an abnormal ST Index *during* exercise (abnormal slow upsloping ST depression defined as 1.0 mm. or greater ST depression with the ST depression in mm. exceeding the ST slope in mv./sec.). Patients who have a clearly normal ST Index during exercise (a normal upsloping ST segment) followed by an abnormal ST depression late postexercise are likely to have normal coronary arteriograms (Fig. 1). These patients with false positive responses are commonly observed to have labile ST or T wave changes with hyperventilation as well. We routinely evaluate the ST segment and T wave response to voluntary hyperventilation and the standing position prior to the exercise test.

Another criterion for a positive exercise ECG is exercise induced ST segment elevation. Patients with Prinzmetal's angina demonstrate ST segment elevation during spontaneous episodes of chest pain, but only a small number of these patients will manifest an abnormal exercise ST segment response. Exercise induced ST segment elevation is more commonly due to areas of abnormal myocardial wall motion as a result of previous myocardial infarction. Chahine and associates found an 86 per cent incidence of left ventricular aneurysm in patients showing exercise induced ST elevation while only 28 per cent experienced angina necessitating termination of the test.

Exercise induced U wave inversion in patients with a normal resting ECG and in the absence of left ventricular hypertrophy strongly suggests myocardial ischemia. This ECG repolarization phenomenon is more common than generally appreciated, may occur in the absence of ST segment abnormalities, and in our experience is usually indicative of a significant stenosis of the left anterior descending coronary artery. The U wave inversion is difficult to detect during exercise especially at high heart rates and more often becomes apparent in the immediate recovery period when the heart rate is slowing and the baseline artifact is less. It may be a transient change and if not overlooked entirely, it may be mistaken for a terminally inverted T wave. This latter differentiation can best be made by analyzing the exercise ECG before and after the appearance of the U waves to determine the true QT interval at comparable heart rates. Analysis of simultaneously recorded leads is also helpful since U wave inversion is most often isolated to horizontal or X axis leads. A right precordial lead will show reciprocal or upright U waves.

A number of medications are known to influence the ST segment response to exercise. These include digitalis, phenothiazines, quinidine, and propranolol. Digitalis can cause false positive ST segment responses even in the face of a normal resting ECG. Although horizontal ST segment depression of greater than 2.0 mm. has

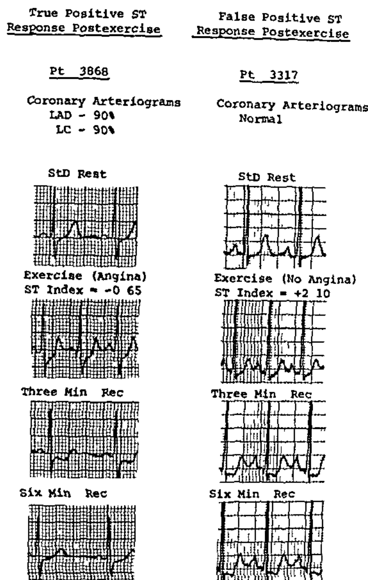


Fig 1 Examples of two patients with horizontal or down sloping ST depression in the postexercise period The computed ST Index for the last 25 QRS complexes during exercise is shown for each patient The ST Index is considered abnormal if the ST (J junction) depression is 1 0 mm or greater and the algebraic sum of the ST depression in milli meters and the ST slope in mv /sec is less than zero (a negative number) Patient 3868 had abnormal slow upsloping of the ST segment during exercise with an ST Index of –0 65 and coronary arteriographic studies revealed 90 per cent stenoses of the left anterior descending and left circumflex arteries Patient 3317 presented with atypical chest pain which was not reproduced during exercise The ST Index during exercise was +2 10 and the patient had normal coro nary arteriograms

been reported to be fairly specific for exercise induced myocardial ischemia in patients taking digitalis,[17] our practice has been to discontinue digitalis preparations for 10 to 14 days when possible if a diagnostic test is deemed important Electrolyte abnormalities such as hypokalemia can also result in a false positive ST segment response during exercise Quinidine, phenothiazines, and propanolol may cause a false negative ST segment response Propanolol may cause conversion of a previously positive ST response to a negative response even when angina is still reproducible with repeat testing[28, 48]

Rheumatic heart disease, left ventricular hypertrophy Wolff Parkinson White syndrome straight back syndrome and mitral valve pro lapse have been described as potential causes of a false positive exercise ECG[8] Prolapse of the mitral valve may ultimately prove to be a common cause of otherwise unexplained false positive ST segment responses to exercise, espe cially in women

When ST segment depression is present on the resting ECG, in the absence of obvious causes such as digitalis therapy left ventricular hyper trophy, or intraventricular conduction defects, an interpretation of the ST segment response to exercise can be attempted by quantitating the magnitude of additional ST depression[28, 49] In patients who present with potential cardiac symptoms the occurrence of 1 0 mm or more of additional ST depression with exercise appears to be a fairly reliable indicator of underlying coro nary artery disease[50] The specificity of these criteria in asymptomatic patients who present with repolarization abnormalities at rest has not been adequately tested In our own experience over 50 per cent of asymptomatic subjects who demonstrate false positive ST segment re sponses to exercise also demonstrate labile ST or T wave changes in the postprandial state or with hyperventilation Thus in patients with resting ST segment abnormalities, every attempt should be made to determine if these changes are labile or fixed Such determinations may ultimately prove to be useful aids in interpreting the clinical significance of a positive ST segment response to exercise in an asymptomatic subject

There appears to be an increased incidence of false negative ST segment responses to exercise in patients whose resting ECG shows an old myocardial infarction pattern[8, 49] However, neg ative conclusions concerning the usefulness of the exercise ECG as a diagnostic test based on such observations are inappropriate In patients with unequivocal myocardial infarction patterns on their resting ECG the diagnosis is already estab lished and the presence or absence of ST depres sion with exercise will give the physician no further diagnostic information

Clinical value of treadmill exercise testing in the diagnosis of coronary artery disease

The multistage treadmill exercise test is clearly beneficial in the evaluation of the patient with known or suspected coronary artery disease The reported results relative to the sensitivity and specificity of the exercise ST segment response will obviously vary according to the patient population studied the exercise protocol used testing endpoints criteria for significant coronary stenosis the monitoring lead system and the ST segment criteria used for a positive test The reported prevalence of abnormal ST segment responses to exercise in symptomatic patients with cineangiographically documented coronary artery disease has ranged from 54 to 85 per cent [28] Virtually all of these reports dealt exclusively with horizontal or downsloping ST segment criteria and other repolarization abnormalities such as slow upsloping ST depression ST elevation and inverted U waves were not considered In our own experience one or more of these repolarization abnormalities are observed in 88 per cent of patients with exertional angina and a normal resting ECG when the patient experiences his usual chest discomfort during the exercise test In patients presenting with a history of one or more episodes of spontaneous chest pain consistent with myocardial ischemia but not with a history of exertional angina the likelihood of obtaining an abnormal ST response is considerably less than 88 per cent if the patient s chest pain is not reproduced during exercise This fact is not surprising when one considers the fact that an abnormal ST segment response with exercise is a reflection of myocardial ischemia and not the coronary anatomy The simple truth is that advanced coronary artery disease is not always associated with stress induced myocardial ischemia

We should emphasize at this point that the reproduction of a patient s usual chest pain during exercise is not by itself a reliable indicator of myocardial ischemia In the absence of ST segment abnormalities the physician should always observe for other diagnostic aids such as an abnormal blood pressure response or postexercise auscultatory changes such as a new S_4 gallop Patients with coronary disease and stable exertional angina will almost always develop their chest pain at the same time of exercise or at the same heart rate–systolic blood pressure product with a serial testing Patients with exercise induced chest pain from other causes tend not to have reproducible pain patterns

The reported incidence of false positive ST segment responses with exercise in symptomatic patients who have normal coronary cineangiographic studies has been fairly consistent at about 10 per cent [28] In our laboratory we observe false positive responses in about 7 per cent of males and 14 per cent of females with an over all incidence rate of 9 per cent However as stated earlier the incidence of otherwise unexplained false positive ST responses can be reduced considerably through specific efforts to detect those patients prone to labile repolarization changes at rest The physician may still elect to exercise these patients to evaluate their exercise tolerance or their risk for potentially significant rhythm disturbances or abnormal hemodynamic responses However the abnormal ST response with exercise cannot be interpreted with any degree of reliability in the presence of labile ST or T wave changes at rest In our experience the majority of these patients do not have significant coronary artery disease when coronary cineangiographic studies are performed

There is a definite correlation between the number and location of arteriographically demonstrated coronary arterial lesions and the exercise ST segment response [23, 1] In our series of 112 patients [8] the incidence of abnormal ST segment responses on a modified V_5 lead system was directly proportional to the number of arteries involved (> 75 per cent stenosis) All patients developed clinical angina during exercise testing and all had a normal baseline ECG Patients with significant coronary disease confined to either the right or left circumflex coronary arteries (single vessel disease) demonstrated only a 44 per cent (8 of 18) incidence of positive ST segment responses Those patients with isolated involvement of the left anterior descending artery showed a 77 per cent (13 of 17) incidence of positive responses The combination of any two involved vessels increased the incidence of a positive response to 91 per cent (49 of 54) There was a 100 per cent incidence of positive responses in 23 patients with severe three vessel disease Our incidences are slightly higher than those reported by others The differences can probably be accounted for on the basis of our use of the computer generated ST Index during exercise the inclusion of only

patients with a normal resting ECG who experience angina during exercise, the use of an endpoint beyond the first appearance of chest pain and our inclusion of only patients with 75 per cent or greater coronary arterial lesions

Thus the results of the exercise ECG must be applied to the clinical situation A patient with a normal resting ECG no labile repolarization changes an abnormal repolarization change with exercise and exercise induced chest pain can be expected to have significant coronary artery disease with a 95 per cent predictive accuracy Furthermore the majority will have multiple vessel coronary artery disease This specificity is sufficiently high to allow further therapeutic decisions to be made on the basis of an over all assessment of the test results (exercise duration or tolerance the exercise heart rate at onset of symptoms or ST depression the magnitude and duration of ST depression, the blood pressure response etc) When the patient has an abnormal resting ECG or is on medications known to cause false positive or false negative tests, or when chest pain is not reproduced during exercise then the reduced sensitivity and/or specificity of the ST response may limit the usefulness of the diagnostic test to varying degrees Under these circumstances, therapeutic decisions will have to be weighted more toward other test results or measured parameters

In a clinically normal subject an abnormal maximal or near maximal treadmill exercise ECG is a risk factor for the later development of overt coronary heart disease Aronow[1] reported that three of 13 subjects with an abnormal ST response to exercise developed symptomatic coronary heart disease in a 30 month follow up period Only one of 87 subjects with a normal test developed symptomatic disease during the same follow up period Bruce and McDonough[5] and Froelicher and associates reported a fourteen fold increase in risk for asymptomatic subjects with an abnormal ST response to strenuous exercise with five and six year follow ups respectively Borer and associates[33] and Froelicher and colleagues[9] reported coronary cineangiographic correlations in highly selected groups of asymptomatic subjects and found that approximately 40 per cent had significant coronary artery disease Ericksson and co workers[11] reported coronary cineangiographic correlations on a group of clinically normal subjects more representative of the general population They found that 64 per cent of the subjects with an abnormal ST response to exercise had significant coronary artery obstruction The vast majority had one or more arteries involved with a 75 per cent or greater stenosis Still the physician must be aware that the predictive accuracy of an abnormal ST segment response to near maximal exercise in clinically normal subjects is not as great as in symptomatic patients Furthermore the natural history of patients with coronary artery disease manifested only by an abnormal ST response to near maximal exercise is unknown Even if multiple vessel coronary disease is demonstrated by coronary cineangiographic studies there is no evidence that their prognosis can be equated to the prognosis of symptomatic patients with similar pathologic anatomy The time of onset of the ST depression along with the depth and duration of ST depression may ultimately prove to be helpful in identifying those patients at greatest near term risk Ellestad and Wan[34] have shown that the duration of exercise and the exercise heart rate attainable by the patient also provide added risk factor information irrespective of the ST segment response

Considering the currently available testing facilities it would be virtually impossible to apply periodic treadmill exercise testing to the population in general for the purpose of detecting latent coronary artery disease Furthermore the cost to yield ratio would make such an undertaking impracticable even in locales where adequate facilities are available Therefore exercise screening of the asymptomatic population should be reserved for those subjects felt to be at greatest risk based on other clinical criteria With rare exceptions a positive ST segment response should be treated as another risk factor and not a definitive diagnostic finding Intensified efforts should be undertaken to reduce other risk factors which can be altered The subject should also be educated concerning early warning symptoms which he should promptly report to his physician Serial exercise testing to detect new symptoms or earlier appearing and more marked ST depression may also be helpful although the clinical value of such serial testing has not been established The authors believe that this approach can be carried

out by the physician in keeping with the patient s best interest

Arrhythmia detection and therapeutic evaluation

Ventricular arrhythmias at rest or during ordinary daily activities are felt to be a risk factor for future overt heart disease or sudden death [5] With maximal exercise testing the prevalence of exercise induced ventricular arrhythmias in a clinically normal population is consistently between 36 and 42 per cent In the majority of subjects the ventricular arrhythmias are in the form of rare to occasional unifocal premature ventricular complexes (PVC) The reproducibility of these arrhythmias in any given subject during serial testing is only slightly greater than by chance alone In other words occasional PVCs may be seen in virtually any normal subject during very strenuous exercise and they are of no clinical significance The prevalence rate of ventricular arrhythmias during maximal exercise in patients with suspected heart disease is higher ranging from 50 to 60 per cent These patients manifest more frequent arrhythmias at lower exercise heart rates and the arrhythmias tend to be more reproducible on serial testing In a group of symptomatic patients with documented coronary artery disease we have shown the prevalence rate of ventricular arrhythmia to be 29 per cent during sub maximal symptom limiting exercise When the behavior of exercise induced ventricular arrhythmias in symptomatic patients with coronary heart disease is compared with those observed in clinically normal subjects significant differences are observed In clinically normal subjects ventricular arrhythmias are uncommon below 70 per cent of predicted maximal heart rate and frequent PVC (> 10/min) or complex arrhythmias (multifocal or consecutive PVC) are rare at these heart rates On the other hand frequent and complex ventricular arrhythmias at low exercise heart rates are characteristic of patients with far advanced coronary heart disease and ventricular dysfunction Exercise induced ventricular arrhythmias alone should not be used as a criterion for the diagnosis of coronary heart disease but they may be useful diagnostic aids in the face of other abnormal parameters

Exercise testing for ventricular arrhythmias may ultimately prove to be most valuable in defining those patients with known coronary heart disease who are at greatest risk of future sudden death Exercise testing and continuous ECG monitoring have both been shown to be more effective than a resting 12 lead ECG for detecting potentially lethal ventricular arrhythmias [6] It is presently not clear which method is more effective especially when time and cost factors are taken into consideration Exercise may provoke arrhythmias by producing an increased demand for myocardial oxygen consumption in patients with ischemic heart disease This results from the exercise induced tachycardia increases in circulating catecholamines and increases in afterload Lown and co workers compared the effectiveness of exercise and 24 hour ambulatory monitoring for exposing patients prone to ventricular arrhythmias They found that arrhythmias which persisted for at least two hours during continuous monitoring were also detected during exercise testing They felt the persistent forms of ventricular arrhythmias correlated best with severe multivessel coronary artery disease Exercise testing may therefore prove to be the more applicable method for exposing those ventricular arrhythmias which are meaningful from a prognostic standpoint

When antiarrhythmic drugs are being used in an attempt to suppress ventricular arrhythmias serial exercise testing can be very useful in assessing adequacy of suppression The test results are immediately available and the need for therapeutic manipulations can be determined during a single patient visit

Exercise testing for functional evaluation

In the clinical management of patients with known cardiac disease a quantitative measure of the patient s functional or performance capacity is most desirable Treadmill testing is useful in this assessment An individual s maximal exercise capacity is defined as the level of exercise required to raise his oxygen consumption ($\dot{V}o_2$) to a peak value which fails to increase further with further increments in work load The maximally attainable Vo_2 (Vo_2 max) declines with advancing age and is reduced to varying degrees in patients with significant cardiac disease The Vo_2 max can be estimated by means of a nomogram which relies on data relative to the subject s age his daily

activity status and his duration of exercise [illegible] The subject is presumed *to demonstrate a functional* aerobic impairment if his duration of exercise falls short of the predicted range of normal Unfortunately the VO_2 max cannot be reliably predicted in individual patients with cardiac disease when symptom limiting endpoints are used [17] In this population the subjective discomfort which accompanies exhaustive exercise and myocardial ischemia greatly affects the patient s motivation and exercise duration

The oxygen consumption resulting from various recreational and occupational activities has been determined [illegible] Data for oxygen consumption requirements are also available for various treadmill work loads Using this data an individual exercise prescription can be developed for the patient with symptom limited heart disease The prescription *can be utilized to advise the patient* concerning the day to day activities he should *avoid as well as in outlining a therapeutic exercise* training program for him

The basal metabolic oxygen requirement for an individual has been arbitrarily designated as a unit of one MET The increases in oxygen *consumption associated with various activities* are quantitated in terms of MET increases over the basal state Patients who fall into New York Heart Association Functional Class I are able to perform oxygen consumption tasks equivalent to 6 to 10 METS without limiting symptoms Functional Class II patients can achieve 4 to 5 METS *Class III* patients *2 to 3 METS* and *Class IV* patients 1 MET The functional capacity of patients with organic heart disease can be estimated with a fair degree of reliability from the clinical history alone but a more reliable and quantitative estimation can often be obtained through graded exercise testing

*Multistage treadmill exercise testing is espe*cially useful in guiding the initial therapy of a patient with ischemic heart disease and exertional angina by providing an objective measurement of his exercise tolerance time and his blood pressure and heart rate responses to exercise A patient with only a moderate reduction in exercise time *and a normal* blood pressure–heart rate response can be expected to benefit from nitrate therapy alone The patient with an exaggerated blood pressure response and/or an accelerated chronotropic response may experience a *significant* improvement in symptoms with beta adrenergic blocking agents even when his initial exercise tolerance time is markedly impaired [16] The appearance of an exercise induced ventricular S_3 gallop or pulmonary *rales after exercise* usually suggests marginal ventricular compensation and may represent a contraindication to the use of beta adrenergic blocking agents An extremely poor exercise tolerance with the onset of angina after a short duration of exercise and at a low heart rate is often associated with a poor or inadequate *response to medical therapy In* general these patients should be considered as candidates for earlier coronary arteriography and possible surgical intervention The occurrence of a sustained decline in heart rate [illegible] or blood pressure[illegible] during graded exercise testing is suggestive of severe multivessel coronary artery disease and *acute, ischemic cardiac decompensation Patients* demonstrating these abnormalities should also be *considered candidates for further diagnostic* evaluation

A comparison of the time of onset of chest pain during a baseline treadmill exercise test to that during follow up testing after a medical or *surgical intervention aids in the objective* evaluation of the therapeutic result This approach has proved to be more objective and reliable than a subjective assessment of the patient s symptoms

Stress testing is definitely contraindicated in the patient with acute myocardial infarction *However a modified exercise test* using minimal work loads may be helpful in assessing residual ischemic symptoms and the capacity to perform ordinary activities in a select group of patients with myocardial infarction during their convalescent period prior to discharge [6] A modified protocol should be chosen which will allow the patient to attain gradually an exercise heart rate of 60 per cent of predicted maximal not to exceed 130/minute Prior to enrolling a recent myocardial infarction patient in a physical conditioning program a graded *submaximal exercise test* is advisable to document his baseline physical work capacity and to demonstrate any tendency toward exercise induced ischemia and/or arrhythmias In the late convalescent period exercise testing can be of use to assess the patient s physical work capacity and his ability to return to employment The demonstration of a good exer

cise tolerance may be helpful in relieving a patient's anxieties and give him the stimulus to return to his previous level of activity

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Cardiac pacing and pacemakers IX
Statistical analysis of pacemaker data

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In the recent past a variety of prosthetic medical devices such as cardiac valves and implantable cardiac pacemakers have been introduced It has become important to analyze the duration of function of these devices as distinct from survival of the patient in whom it is implanted The longevity of the device may be less than that of the patient or may have residual survival capacity after the patient s death The device (especially a pacemaker) may be removed for reasons such as infection unrelated to its longevity capability

The development of a data base of medical devices and a statistical technique for its analysis is important to ascertain longevity periods for more intense observation prophylactic replacement and demonstrate the superiority of one model or pacing mode compared to another Only implantable pacemakers will be the subject of this report Because of rapid technologic development a variety of different power sources (nuclear mercury-zinc lithium) and different circuitry (discrete hybrid and digital) it is important to be able to compare the performance (defined as longevity and failure pattern) of models manufactured simultaneously or successively Further it is important to provide the professional user with use data which is presented in an identical way and therefore allows direct comparison between different models

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Pioneering work has been done for the past ten years by a variety of workers in providing carefully recorded and analyzed data concerning pulse generator longevity That data is even more important now because of the large number of patients and the statistical guidance required for their management An appropriate computer data base can absorb the large amount of data generate the analysis and provide a printout sufficiently frequently to be of real assistance in a pacemaker program

The survival of the patient with an implanted pacemaker can be similarly defined separately from that of the pulse generator this knowledge is invaluable to ascertain the longevity requirement of pacemakers to be manufactured

Each pulse generator implanted at Montefiore Hospital and Medical Center is recorded by model and serial number its date of implant and explant and the patient in whom implanted The generator is followed throughout its duration in the patient and upon removal is analyzed The cause for removal is then coded four possibilities of explant exist

1 The patient may have *died* and the pacer is known to be functioning normally or at least is not believed to have caused the patient s death A major effort is made in all deaths to ascertain cause and the involvement if any of the pacemaker The pacer is credited with normal function for its period of use and is then removed from the series

2 The patient *lost to follow up* is a circumstance treated as No 1 above with the date of loss assigned to determine a period of known normal function

3 The pacer has been *replaced* but *not because*

DR SEYMOUR FURMAN S FACEMAKER FILF MODEL 143A LISTED ON 11/?5/75

UNIT $	FATIENT	IMFLANTED	EXFLANTED	CODE
101	M[redacted] M	6/23/69	11/2/71	I-IIAT
107	K[redacted] A	7/15/69	8/19/71	D-IIAT
108	A[redacted] I	7/17/69	9/2?/71	D-IIAT
102	W[redacted] R	7/24/69	3/23/71	D-IIA
118	N[redacted] M	7/29/69	9/22/71	D-IIA
112	A[redacted] S	7/29/69	7/?1/71	D IIA
137	B[redacted] A	8/14/69	1/1/71	L-?
116	H[redacted] F	8/22/69	1?/2/71	D-IIAT
104	P[redacted] J	9/4/69	8/17/71	D-IAT
150	N[redacted] C	9/18/69	12/8/71	E-IIC
146	H[redacted] R	9/25/69	7/15/71	I-IIAT
1?0	H[redacted] A	9/26/69	5/26/7?	D IIAT
?46	S[redacted] F	1?/3/69	8/1/?0	R-CEASED
?39	Z[redacted] R	1?/10/69	4/4/?2	D IIAT
17?	B[redacted] C	1?/11/69	8/18/72	D-IIAT
223	C[redacted] R	1?/?3/69	6/5/74	D-IIAT
177	L[redacted] M	1/6/70	4/12/73	D-IIAT
194	F[redacted] T	1/9/70	1/1/71	L ?
184	L[redacted] A	1/9/70	8/?/73	D-IIAT
3?3	Y[redacted] L	2/17/70	1/??/72	R-IID
183	M[redacted] G	1/26/70	8/25/72	D-IIAT
198	S[redacted] S	1/13/70	1/7/72	D-IIAT
321	K[redacted] M	2/5/70	4/6/70	R CEASED
330	B[redacted] D	2/6/70	12/5/7?	D-IIAT
??4	S[redacted] B	2/12/70	3/30/73	D-IIAT
438	K[redacted] P	3/2/70	7/5/72	D IIA
393	D[redacted] J	3/4/70	3/19/71	D-IIA
342	C[redacted] R	3/5/70	7/16/71	D-IA2
268	B[redacted] E	3/10/70	10/23/70	R-CEASED
349	M[redacted] J	3/12/70	1/4/73	D IIAT

Fig 1 Computer generated pacemaker file for Cordis ventricular inhibited model 143A now obsolete Each unit is listed by serial number name of patient in whom implanted dates of implant and explant and explant code *D* is removal for generator failure *IAT* = cessation of pacing detected by telephone *IA2* = major pacing change (i e rate change by more than 10 BPM) but with consistent capture detected in pacer clinic *IIA* = impending failure detected in pacer clinic *IIAT* = impending failure detected via telephone monitoring *L* = lost to follow up at the date indicated *R* = removed for reasons other than pacer failure *R ceased* = patient died pacer functioning *E* = electively removed—no pacer failure

IF SEYMOUF FURMAN S LIFE TABLE FOR PACEF MODEL 143A CALCULATED 11/2?/75

AGE MONTHS	NUMBER ENTEF	===REMOVALS=== FAIL	ELCTV	UNFEL	LOST-TO FOLLOW	PART EXFOS	-% SURVIVAL RATE - INTERVAL	CUMULATIVE	STANDARD EFFOR
0 - 3	100	0	0	3	0	0	100	100	0
3 - 6	97	0	0	4	1	0	100	100	0
6 - 9	92	1	0	3	0	0	98 895	98 895	1 09885
9 - 12	88	0	0	0	1	0	100	98 895	1 09885
12 - 1?	87	2	0	1	0	0	97 ?878	96 6084	1 9251?
15 18	84	2	1	4	1	0	97 5308	94 2229	? 51001
18 ?1	76	3	0	1	0	0	96 0265	90 4789	3 ?0877
?1 ?4	72	4	1	2	0	0	?4 3262	8? 3454	3 9?116
24 - ?7	65	5	2	3	0	0	90 4	?? 1?22	4 7622?
?7 - 30	?4	7	0	3	0	0	8? 6666	66 065?	5 48954
30 33	44	6	0	0	0	0	86 3636	57 7472	5 86893
33 - 36	38	?	0	1	0	0	86 6666	?0 0475	6 01227
3? - 3?	32	7	0	1	0	0	77 7777	38 9??8	5 9674?
39 - 4?	?1	3	0	1	1	0	86 ??45	33 8485	5 86504
42 4?	17	4	0	?	0	0	77 7777	?6 3?66	5 64008
4? - 4?	13	3	0	0	?	0	7?	1? 74?	5 35936
48 ?1	8	4	0	0	0	0	50	? 87248	4 40045
?1 ?4	4	1	1	1	0	0	66 6666	6 58165	3 97818
?4 - ?7	1	1	0	0	0	0	0	0	0
		?9	?	30	6	0	= 100		

Fig 2 Life table tabulation by 3 month intervals for Cordis 143A All implanted are entered at time zero Each unit removed is listed as *failed elective* or *unrelated* The per cent survival rate is listed for the *interval* i e the per cent of those units entering an interval which leave it intact The *cumulative survival rate* is that for the entire series The duration in months of one *standard error* is listed

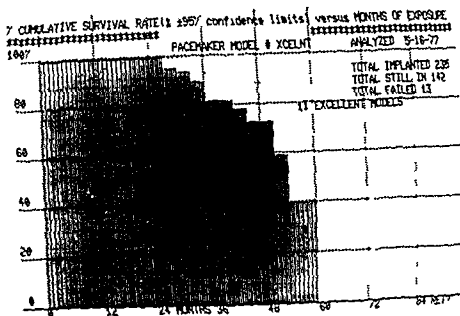


Fig 3 *Excellent* — One hundred per cent survival for 24 months With onset of failures the ± standard error limits are indicated There is 90 per cent cumulative survival rate 91 to 54 months after implant and a 40 per cent rate at the end of 60 months (Unretouched photograph from cathode ray tube screen)

of failure perhaps for infection or change in pacing mode this possibility too is treated as No 1 above

4 The pacer has *failed* and has been removed or (rarely) has caused the patient s death (The pacer is credited with normal function and then failure)

Another code (S) is that for *continued function* in a living patient When all generators have been removed this coding no longer exists for a series

It is important that the derivation of this data be based on and be supported by an extensive and careful follow up technique (*see* Cardiac Pacing Pacemakers VIII) in which patients are monitored as carefully as possible each event is evaluated and each removed unit is analyzed in an electronics laboratory to ascertain function and assess the accuracy of clinical judgement

A short printout is provided to the pacemaker staff monthly Additional data are available at all times (though the computer is not on line it is controlled by the pacemaker staff) and specific comparisons not routinely provided are made available as necessary All pulse generators used at Montefiore Hospital and Medical Center since mid 1969 are included in the data base The monthly printout is only of those models with units still implanted and functioning though older inactive models are retained in the data base and the data are retrieved as necessary

More than 85 different models from 13 different manufacturers encompassing over 2 300 pulse generators have been recorded Data is updated weekly and calculated on a monthly basis In addition to the abbreviated monthly printout a more complete printout is provided quarterly which includes the full data base and analysis and is provided to all pacemaker surgeons cardiologists nurses and engineers Each manufacturer is provided with his own data (and his own data only) quarterly

The monthly and quarterly analyses *include*

1 A printout of all pulse generators listed by model and serial number date of implant and explant and reason Each pulse generator is listed individually (Fig 1)

2 A verification list of all pulse generators by ascending duration of implantation

3 A life table with the cumulative survival rates the interval survival rates and standard errors (Fig 2)

4 A graphic display of the life table with 95 per cent confidence limits

Mathematical and computation technique

Various statistical analyses have been used to record analyze and estimate pulse generator longevity We have used the actuarial method which has earlier been used to evaluate the longevity of prosthetic cardiac valves and cardiac pacemakers[8-10] Since the beginning of the computerization program during September, 1974, a similar statistical method has been adopted by the Association for the Advancement of Medical Instrumentation as a suggested *standard*[11] *The* calculations are similar except for that of the *lower confidence limit*

The actuarial method accurately estimated the depletion of a population in time The 'estimator of survival is the *CUMULATIVE SURVIVAL RATE* at any desired time and that in turn is based upon *INTERVAL SURVIVAL PROPORTIONS,* P(k) as defined

$$P(k) = 1 - \frac{D(k)}{N(k) - \frac{S(k)+L(k)+R(k)+E(k)}{2}}$$

where *D* = number failures (either battery exhaustion or electronic failure) in Kth interval

N = number entering the Kth interval,

L = number lost to follow up in Kth interval

E = number electively removed in Kth *interval*

R = number non pacer related failures in Kth interval

S = number surviving an incomplete interval

and *k* = quarterly interval since implantation

The *CUMULATIVE SURVIVAL RATE* Q(k) is equal to the product of all previous Interval Survival Proportions or mathematically

$$Q(k) = P(1) \times P(2) \times P(3) \quad P(k) \times 100$$

Therefore the *CUMULATIVE SURVIVAL RATE* is the probability of a pacemaker surviving to a particular time based on the previously observed survival experience This method offers a precise means of estimating the Kth quarterly *SURVIVAL PROPORTION by utilizing* information from patients with less than K quarterly intervals of experience Two assumptions have been adopted One is that pacemakers *LOST TO FOLLOW UP* are presumed *to have* the same natural history as those still followed With this assumption the maximum information is extracted from the raw data without biasing the results toward or against the actual longevity Another assumption *is that pacemakers surviving* an incomplete interval contribute on the average *one half* an interval of experience This assumption *is justified by the equal* distribution of implantation and removal of pacemakers over each three month interval The primary result of these statistics is the LIFE TABLE (Fig 2) It *consists of a compilation of all data necessary* to compute the *CUMULATIVE SURVIVAL RATES* and is tabulated in quarterly intervals The Standard Error of the Cumulative Survival Rate is an estimate of precision for the corresponding quarterly Cumulative Survival Rate The Standard Error SE(Q(k)) is defined

$$SE(Q(k)) = Q(k) \times \sqrt{\frac{1-P(1)}{N(1) - \frac{S(1)+L(1)+E(1)+R(1)-D(1)}{2}} + \quad + \frac{1-P(k)}{N(k) - \frac{S(k)+L(k)+E(k)+R(k)-D(k)}{2}}}$$

Another result, the *SURVIVAL CURVE* is a plot of the *CUMULATIVE SURVIVAL RATE* against exposure time The *SURVIVAL CURVE* is valuable because of its visual impact, especially when two curves are compared and the 95 per *cent confidence limits are indicated*

We use the Normal Theory to define the 95 per cent *CONFIDENT LIMITS* as

$\pm$ 95%C L = $\pm$ 2 × STANDARDERROR(K)

The results are comparable to the AAMI Technique when the data base is over 20 units

All data and calculations are on a PDP 8 E *minicomputer** equipped with 32K of core memory, an RK8E Disk a TD8E Dectape and LA 36 printer and a *VT 55 graphics terminal* The programs are written in the Basic language under the OS 8 operating system

Comparison of pulse generator quality

Analysis of the longevity of implanted cardiac pacemakers is required to evaluate the operational characteristics of competing power sources and to establish a criterion of manufacturing quality *independent of* features and based on specific longevity and failure characteristics

*Digital Equipment Corporation Maynard Mass.

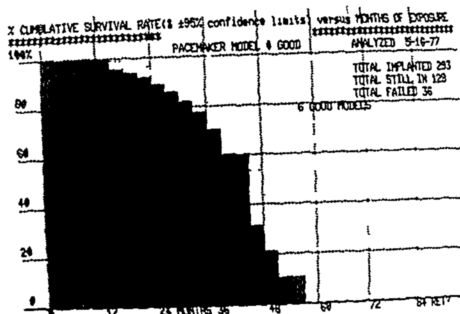


Fig 4 *Good* — Failure begins earlier than in the excellent series and continues more rapidly There is 50 per cent survival 48 to 51 months after implant No units have reached the sixtieth month (Unretouched photograph from cathode ray tube screen)

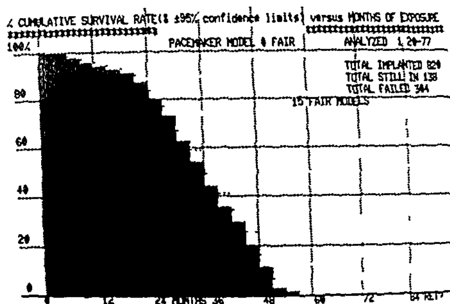


Fig 5 *Fair* — Failures appear after the first six months of implant and the cumulative survival falls rapidly There is 50 per cent survival 36 to 39 *months after implant All* units have failed by the 57 to 60 month (Unretouched photograph from cathode ray tube screen)

These characteristics include the absence *of early* failures when power capacity should not be a factor the appearance of the first wear out fail ures and the magnitude of the ongoing *or ran* dom" failure rate

To ascertain the level of quality of pacemakers implanted since 1969 four levels of quality were established arbitrarily The data are relevant as of May 1977

These are

Excellent The pulse generator model should demonstrate 100 per cent function for at least 24 months (Fig 3)

Good Ninety eight per cent cumulative surviv

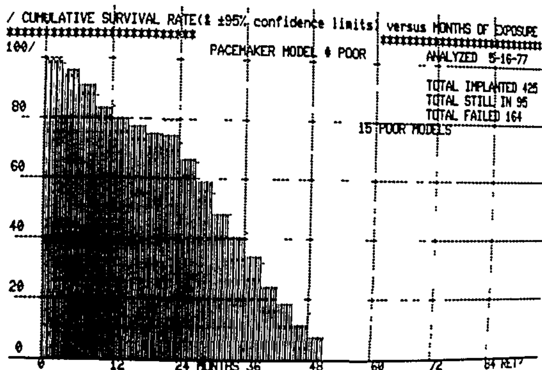


Fig 6 *Poor* = Failures begin during the first three months after implant Cumulative survival falls very rapidly There is 50 per cent survival 30 to 33 months after implant All units have failed by the 51 to 54 month (Unretouched photograph from cathode ray tube screen)

al demonstrated 12 to 15 months after implant, over 90 per cent at 18 to 21 months, and over 80 per cent at the end of two years (Fig 4)

Fair Over 90 per cent cumulative survival at 12 to 15 months, or under 75 per cent at 18 to 21 months or under 50 per cent at the end of two years (Fig 5)

Poor Under 90 per cent survival at 12 to 15 months, or under 75 per cent at 18 to 21 months or under 50 per cent at the end of two years (Fig 6)

Two additional displays compare the long term 1969 to 1977 quality of all non nuclear models of two major manufacturers As these two graphs include a long period of observation they are less affected by a single good or bad model and represent long range manufacturing performance (Fig 7, *A* and *B*) These data show that one manufacturer has provided substantially poorer quality over the past eight years Obviously, the present situation is not clear from these data which clearly define the former situation

Comparison of lithium and mercury-zinc power sources

Perhaps the most eagerly anticipated event in pacemaker technology is that of the change from a mercury-zinc power source to a lithium source The first lithium pacemakers were implanted in 1973,[1] and a few have, consequently, reached the fourth year of use Comparison of the longevity of all of the mercury-zinc and lithium units rapidly reveals the distinctly better behavior of the lithium and the statistically significant difference of the two power sources (Fig 8)

Another technical change, from discrete component design to hybrid circuitry, has been accompanied by a number of early failures Analysis of the longevity of hybrid and discrete pulse generators of one manufacture with the same (mercury-zinc) power source indicates very well the early failure rate with both and that with the overlap of standard error the two were identical until the thirty fourth month of use, then the superiority of the hybrid circuitry becomes distinct, only to be lost in statistical insignificance during the fiftieth month after implant (Fig 9)

Equally the rate of current drain from a mercury-zinc battery has been thought to be a significant factor in the longevity of the pulse generator the slower the drain the longer the life Two groups of generators have been compared one with a fixed and relatively high current drain the second with a variable and as used a very low output The effect of low current drain becomes immediately apparent with a statistically significant difference between the

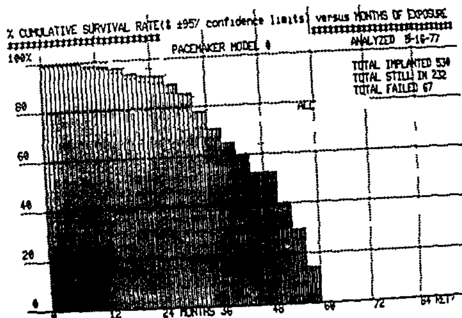


Fig 7 A and B Comparison of two pacemaker manufacturers Note that in one manufacturer (A) 2 per cent of units failed during the first year the 50 per cent survival time was during the 51 to 54 months and the last failure occurred after the sixtieth month In the other (B) only 90 per cent survival exists at one year the 50 per cent survival was during the 30 to 39th month after implant and the last failures occurred during 57 to 60th months after implant (Photographs from cathode ray tube screen Identification deleted)

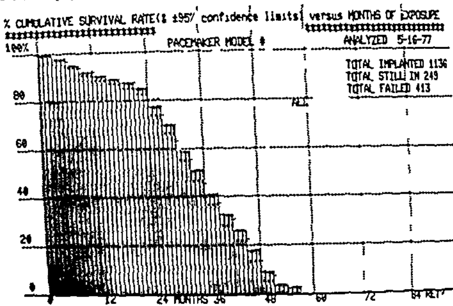


Fig 7B For legend see preceding page

two at the thirty sixth month following implant The lower drain is clearly associated with prolonged longevity (Fig 10)

Patient longevity

The longevity of patients following pacemaker implant is of course a function of factors unique to each patient and each disease process Nevertheless as for the calculation of the life table for the general population and for patients with other disease processes the longevity calculations using the life table technique are valuable

The pacemaker population survival can be

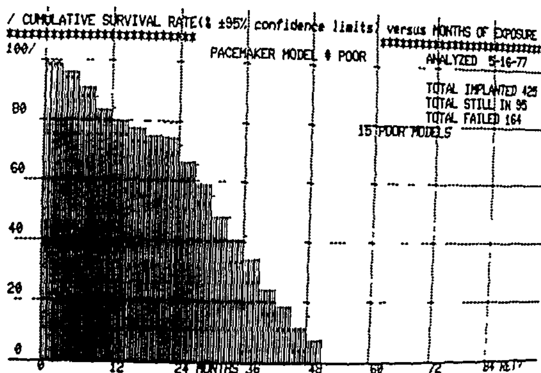


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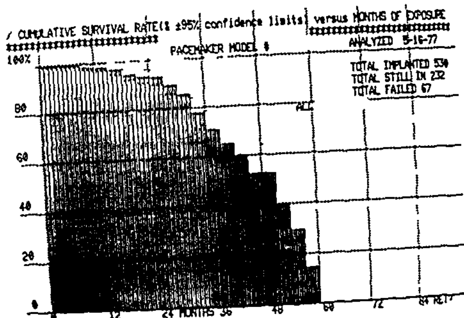


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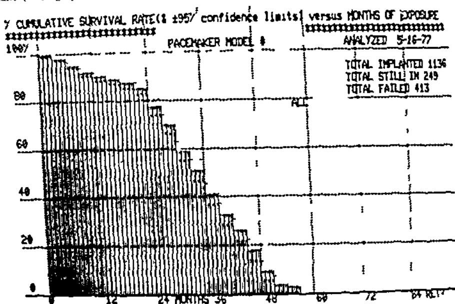


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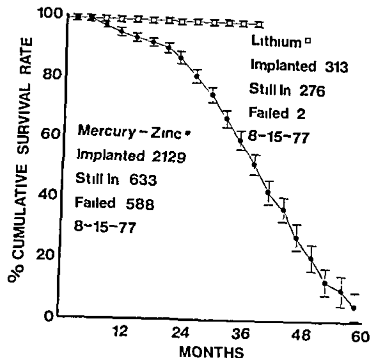


Fig 8 A comparison of the longevity of all mercury-zinc pacemakers used since 1969 and of lithium units used since 1974

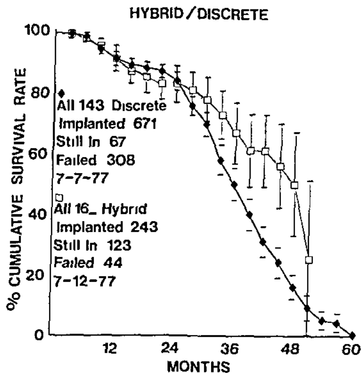


Fig 9 Comparison of hybrid and discrete circuits from a single manufacturer both using mercury-zinc batteries Note little change in survival with the newer circuitry though a significant improvement does exist between the 33 and 51 months

calculated for a variety of segments Implantation of pacemakers is readily calculable since 1962 Calculations have been made over a period of 14 years to the end of 1976 and several different approaches have been used

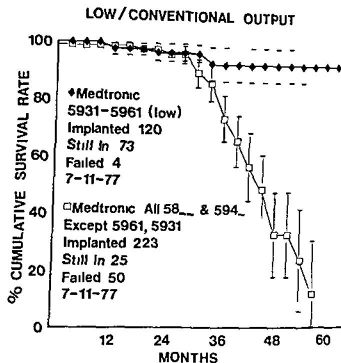


Fig 10 The benefits of reduced battery drain Both series are from the same manufacturer both with mercury zinc batteries A significant difference in survival occurs at the 36th month following which the difference in survival patterns becomes progressively more pronounced

The simplest analysis is that of the proportion of patients implanted by decade of age at implant and then further subdivided into male and female This analysis shows that 40 per cent of all patients with pacemakers are initially implanted between the age of 70 to 80 years that age 60 to 70 accounts for about 21 per cent and age 80 to 90 for 25 to 30 per cent that 3 8 per cent are under 50 years of age and that 2 6 per cent are over 90 years of age and that at each age more men are implanted than women (Fig 11)

This disparity of men over women is then confirmed by the calculation of the implant percentage with men and women weighted to their representation in the population Each pair of bars represents the percentage of each sex implanted of the total at that age group and corrected for the proportion in the population (Fig 12)

Patient survival can be compared to the survival of the general population in the U S A As a broad representation of over 90 per cent of all patients (only those under 65 years of age were eliminated) comparisons were made to population longevity at 70 years and 76 years Comparison of patients of 65 to 75 with that of the general population at age 70 indicates an almost identical

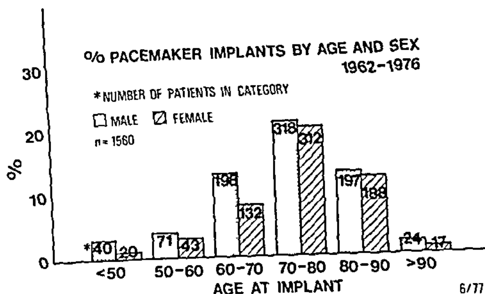


Fig 11 The ratio of pacer implants by age and sex A pleurality of patients is between 0 and 80 years of age

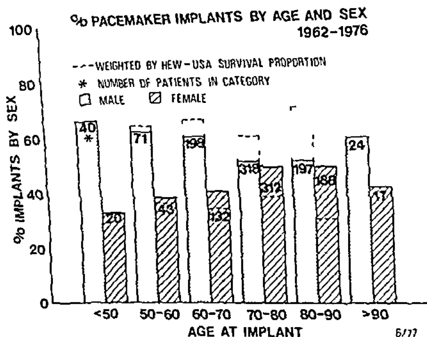


Fig 12 The ratio of pacer implants by age and sex weighted by the ratio of men to women during each age group As there are more women than men at each age group the actual incidence of arrhythmias requiring pacer implant is greater for men during each period

survival to the eleventh year when statistical significance ceases

The older patient group i e all those 75 to 100 years at implant have a significantly superior survival compared to age 76 for the general population after the fifth year following implant (Fig 13)

Calculation of patient survival by age groups and the survival of the full group (from 0 to 100 years) displays the survival of the entire popula

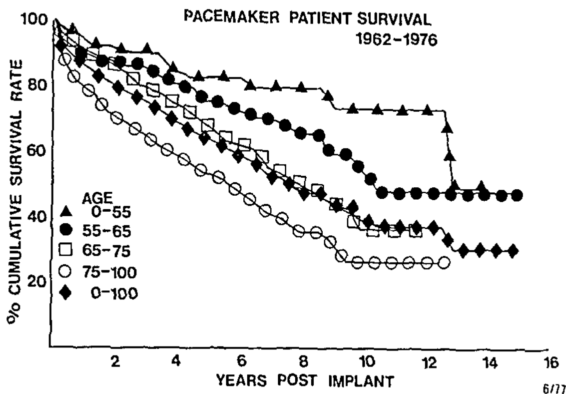


Fig 13 Patient survival by various age groups As may be expected the younger the patient the more favorable the outlook

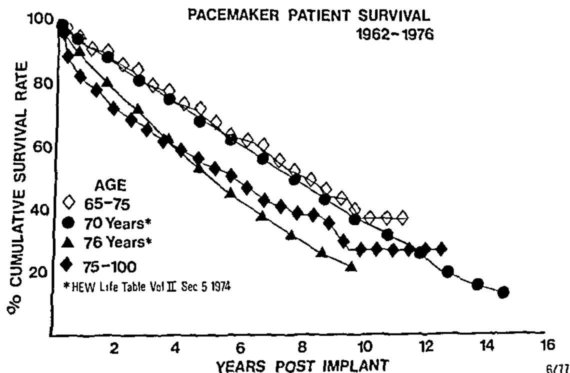


Fig 14 Patient survival compared to the life expectancy in the U S A Pacer patients have the life expectancy of the general population and there is a suggestion (though not statistically significant) that survival may be even better

tion of pacemaker patients and of each population segment The data, as expected show the youngest patients with the greatest survival with each succeeding older group with a lessened survival (Fig 14)

Many more displays are possible i e for men compared to women at all ages for specific arrhythmias for all patients as a function of intercurrent disease etc Obviously these data are invaluable for selection of appropriate hardware

to be implanted and for planning for health services and insurance costs

At the present time patient needs require the maintenance of data concerning the operation of prosthetic devices clinic operation requires hard data concerning longevity and failure patterns to determine follow up patterns regulatory agencies require that data to be aware of the actual state of the art manufacturers need it to evaluate their efforts and third party insurors require it to calculate cost projections Only a computer based carefully maintained statistical survey can provide that information

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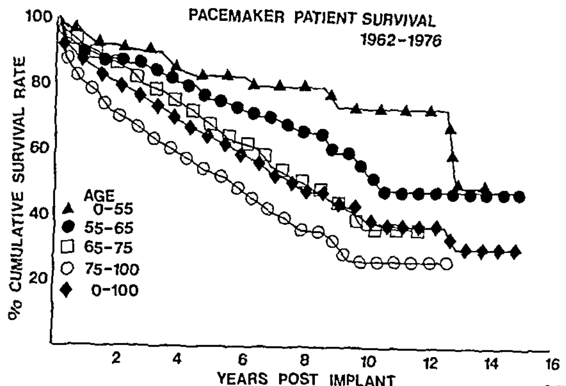


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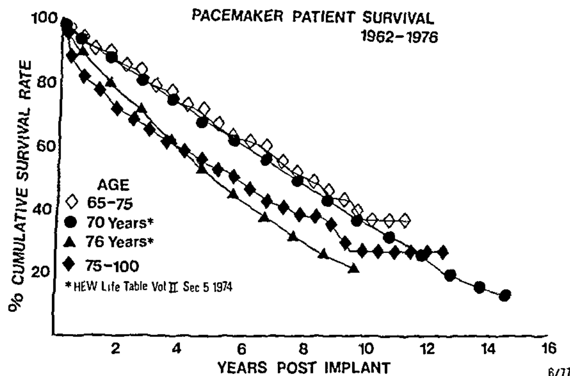


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from chronic ischemia due to the underdeveloped blood upply

Rheumatic valvulitis has occurred in seven cases of single coronary artery In our patient the rheumatic etiology is supported by diffuse thickening of both mitral cusps at the time of surgery and by the presence of microscopic fibrosis The association of rheumatic valvulitis with myocardial infarction in our patient was apparently fortuitous Neverthe less th combination of chronic mitral regurgitation perhaps made worse by a ruptured chorda and left ventricular dysfunction from the myocardial infarction led to congestive heart failure in this patient

In summary myocardial infarction in single coronary artery is quite unu ual and may be due to underdeveloped blood supply with secondary fibrosis

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Laurence R Burwell MD
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Of plastic materials in clinical medicine

The trend toward greater use of plastic materials in clini al practice has advantages and disadvantages The convenience and advantage of discarding plastic devices after use and the assurance of individual use are definite The lack of need to clean and sterilize these materials is a definite cost advantage However there are at least two plastic devices that are important and frequently used in hospitals which are certainly traumatizing and injurious to patients namely the plastic needle and the plastic nasogastric tube Both are traumatizing especially the plastic nasoga tric tube This tube is so rigid and inflexible that it produces pressure necrosis at every turn it makes on its course from the nares to the stomach Even worse its leading edge is often so sharp and so rig i th t it scrapes and tears the surfaces of the nasopharynx as it is passed into the stomach e pecially in the unconscious patient The resultant hemorrhage can be large and the blood is a pirated into the respiratory t a which leads to compli cation associated with choking and the development of a piration pneumonia In a recent instance at a local hospital an area of pressure necrosis in a patient bled so profusely that the patient became exsanguinated as he quietly lay in his bed asleep during the night He was found dead in bed early the next morning There is available the much tested and superior soft Levine rubber nasogastric tube Why not use it? It is a simple and extremely useful and important clinical device but unfortunately some physicians do not know how to use any nasogastric tube

There is a need to learn more about the advantages and disadvantages of plastic clinical devices The devices are all extremely useful and necessary in the practice of medicine but who buys plastic devices and why? We are overly committed to plastics for insufficient reasons Some plastic things are good but many are bad At least let s not use those that hurt our patients

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Single coronary artery with myocardial infarction and mitral regurgitation

Single coronary artery without other congenital cardiac defects has been thought an interesting but unimportant finding because its peripheral distribution is usually adequate for myocardial needs We studied a patient with single coronary artery myocardial infarction and mitral regurgitation

A 45 year old man entered the hospital for congestive heart failure with mitral regurgitation The electrocardiogram and vectorcardiogram showed an old anterior myocardial infarction and atrial fibrillation Cardiac catheterization revealed severe mitral regurgitation with mild pulmonary hypertension Selective coronary angiography showed the right coronary artery to be a large dominant vessel (Figs 1 and 2) Almost immediately after its origin a large branch arose which represented the left coronary artery It coursed posterior to the aorta and divided into a marginal circumflex artery a very small left anterior descending and several diagonal branches which followed the usual distribution (R 2 A in Ogden's classification) No atherosclerosis was seen At surgery the left anterior descending artery was hypoplastic A ruptured chorda tendinea of the anterior mitral leaflet was found The diffusely thickened mitral valve was replaced by a porcine xenograft Microscopic examination revealed focal vascularization consistent with rheumatic valvulitis

Anomalies of the coronary arteries occur in 2 85 per 1 000 autopsies A large series of coronary angiograms yielded an incidence of 1 9 per 1 000 studies Single coronary artery comprises 4 5 per cent of congenital coronary anomalies The number of reported cases has greatly increased with the widespread use of coronary angiograms Myocardial infarction has occurred in 22 cases Of these 15 were male and five were female with an average age of 53 years Fifteen of 22 (73 per cent) patients with infarction had a single vessel originating from the right sinus which is unusual since single coronary arteries generally originate equally from the right and left sinuses of Valsalva Angina pectoris with ischemic ST segment depression may occur with a single coronary artery in the absence of atheromatous obstruction Furthermore atrial pacing and measurement of coronary arteriovenous lactate differences have shown ischemic ST segment depression and lactate production in this situation Moreover focal myocardial necrosis and fibrosis may be associated with clinical and electrocardiographic evidence of severe myocardial infarction without atheromatous occlusion of coronary arteries when a portion of the myocardium is supplied by a small or hypoplastic vessel

The absence in our patient of atheromatous obstruction in the coronary artery with evidence of myocardial infarction by electrocardiogram vectorcardiogram and left ventriculography led us to conclude that myocardial fibrosis occurred

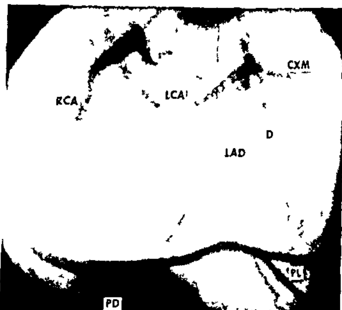


Fig 1 Selective injection of the right coronary artery in the 30 degree left anterior oblique projection *RCA* = right coronary artery *LCA* = left coronary artery *LAD* = left anterior descending *D* = diagonal *CXM* = circumflex marginal *PD* = posterior descending *PL* = posterolateral branches

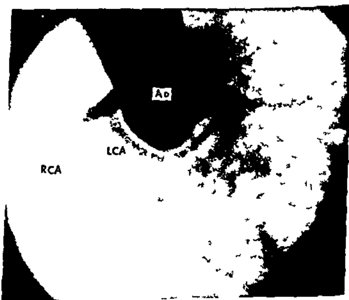


Fig 2 Aortic supravalvular injection in the 30 degree left anterior oblique projection *Ao* = aorta *RCA* = right coronary artery *LCA* = left coronary artery

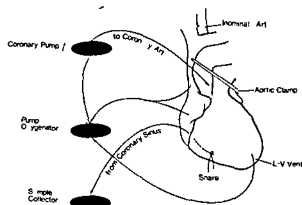


Fig 2 Cardiopulmonary bypass was carried out as in the diagram above Coronary perfusion was maintained through a separate calibrated pump and cannulation of the clamped aortic root A catheter can be seen lying in the coronary sinus for collection of coronary sinus blood and a snare placed around the coronary sinus to assure total blood collection (Reproduced from Engelman R M Chandra R Baumann F G and Goldman R A Myocardial reperfusion a cause of ischemic injury during cardiopulmonary bypass Surgery 80:266 1976

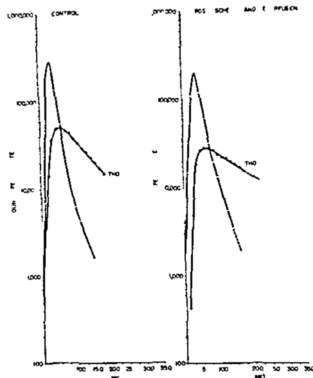


Fig 3 An example of the plotted semilog time concentration curves demonstrates the results obtained between control and post ischemic studies (Reproduced from Engelman R M., Chandra R Baumann F G and Goldman R A Myocardial reperfusion a cause of ischemic injury during cardiopulmonary bypass Surgery 80 266 1976

subepicardial flow decreased significantly ($p < 0.05$) from 1.10 ± 0.05 to 0.69 ± 0.08 It is apparent that the myocardial tissue most susceptible to ischemic injury secondary to edema formation during bypass is the subendocardial layers a fact long suspected by cardiac surgeons who see subendocardial ischemia clinically The degree of decrease in subendocardial perfusion is especially profound because the normal protective reactive hyperemic response of the coronary bed following ischemia is abolished by this edema formation In the same series of animals the coronary vascular resistance before ischemia was 0.30 ± 0.02 This increased after three ischemic periods to 0.34 ± 0.04 A normal response would be for the resistance to significantly decrease as was noted after the first of the three ischemic periods (Table I)

The development of intraoperative myocardial edema is a serious complication of cardiopulmonary bypass to be avoided whenever possible The means at our disposal include (1) avoidance of ventricular fibrillation (2) restriction of ischemic time and provision for longer reperfusion periods (3) use of cardioplegic hypothermic protection during ischemic arrest (4) avoidance of overperfusion of the myocardium after *ischemia by not using a high perfusion pressure* and (5) utilization of mannitol or other hyperosmolar perfusate to reduce postischemic edema formation The use of one or more of these modalities has sharply reduced the risk of ischemic injury during intracardiac surgical procedures to one to two per cent in most centers

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Table I Coronary vascular resistance

Time period (minutes of arrest)	*mm Hg/mL /min /100 Gm*
Control	0.30 ± 0.02
30	0.20 ± 0.04
60	0.26 ± 0.05
90	0.34 ± 0.04

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Myocardial edema, a complication of ischemic arrest during cardiopulmonary bypass

Ischemic arrest is frequently employed during cardiopulmonary bypass to allow the surgeon to operate upon a quiet bloodless flaccid heart for precise repair of cardiac defects or creation of a small anastomosis The consequences of ischemia include degeneration of capillary endothelial cells[1] and the breakdown of the sodium pump located in the cell membrane This active transport mechanism responsible for *maintaining an intracellular-extracellular sodium gradient* and counterbalancing the osmotic effect of high intracellular colloids stabilizes cell volume With reduction of this transport mechanism due to a decrease in energy support sodium enters the cell and cell swelling occurs With myocardial and capillary endothelial cell swelling and degeneration (Fig 1) a diminution in perfusion occurs preventing nutrient flow from reversing the effects of ischemia despite reperfusion of the myocardial muscle mass Ultimately with repeated ischemic insults considerable edema accumulates resulting in a measurable volume increase in myocardial extravascular water

Using the technique of multiple indicator dilution curves as described by Ramsey and associates for the lung myocardial extravascular water was measured in 11 pigs after three 30 *minute periods of normothermic ischemic arrest interrupted* by 5 minutes of perfusion at 100 mm Hg with the heart fibrillating The experimental model is shown in Fig 2 Myocardial intravascular water was measured using 4 to 5 μCi of radioactive iodinated serum albumin (RISA) and total myocardial water using 50 μCi of tritiated water (THO) Both markers were stimultaneously injected as a bolus into the coronary perfusate and all coronary sinus blood was retrieved in the timed sample collector Coronary sinus blood counts per *minute of RISA and THO were plotted on a log scale against a* linear time scale in seconds (Fig 3) The straight line extrapolation of the exponential descending limb calculated by computer enabled total flow for RISA and THO to be determined using standard formulas The volume into which each indicator was distributed between injection and sampling sites was determined using the mean transit time calculation The difference between RISA and THO volumes corresponds to an approximation of the extravascular water volume

The determination of extravascular water in the heart of control pigs averaged 46 4 ± 1 7 ml /100 Gm This increased significantly ($p < 0\ 05$) to 52 6 ± 2 0 ml /100 Gm in postischemic hearts Associated with the development of myocardial edema was a significant selective decrease in subendocardial perfusion as measured by radioactive microsphere distribution *comparing preischemic (control)* animals with those following ischemia The perfusion ratio of subendocardial/



Fig 1 An electronmicrograph of a heart after ischemia documents *myofibrillar degeneration* enlarged edematous mitochondria (*M*) with broken disarranged cristae and a clear matrix to the point of vacuolization (*V*) Capillary endothelial cells show degenerated organelles and blebs protruding into the lumen (*double arrows*) *arrow* = intercalated disc (Original magnification ×11 000) (Reproduced from Engelman R M Chandra R Baumann F G and Goldman R A Myocardial reperfusion a cause of ischemic *injury during* cardiopulmonary bypass Surgery 80 266 1976

naire *shows that roughly half the country favors* the 2 Gm sodium diet This practice presumably derives from earlier data that demonstrated decreased renal blood flow in congestive heart failure with secondary retention of salt and water This degree of sodium restriction may be dangerous for many reasons principally that in the presence of decreased cardiac output loss of extracellular sodium chloride may further decrease output An argument can also be made against unlimited salt intake since some Americans habitually consume large amounts of salt with their meals and the risk of fluid overload and congestive heart failure in the presence of acute myocardial infarction is real A reasonable compromise would appear to be a no added salt diet which in most hospitals contain 3 to 4 Gm of sodium with alterations made according to clinical status

Over 90 per cent of institutions in our sample have no potassium restriction or supplementation in their CCU diets This is probably due to an appreciation of the lability of serum potassium levels in situations of changing fluid status acidosis, diuretic therapy vomiting and the like with the need for frequent reassessment Potassium liberalization would be helpful in the presence of hypokalemia commonly due to frequent diuretic use while potassium restriction would be appropriate where there is severe hyperkalemia or renal failure No generalization about what constitutes optimal potassium intake is possible

Should bulk be restricted in the Coronary Care Unit diet? Liquid diets may reduce the risk of cardiac arrest by avoidance of the vasovagal and arrhythmia producing effects of gasping or of straining during bowel movements They may also reduce aspiration On the other hand some patients find liquid or low bulk diets constipating and under these circumstances increased bulk may be more desirable Again no universal recommendation regarding optimal bulk in the CCU diet can be made

Lastly the topic of carbohydrate restriction was surveyed Fully 80 per cent of institutions responding did not restrict carbohydrates in the Coronary Care Unit diet We know of no data to support or refute this practice but since glucose has been shown to be an important fuel source for the acutely ischemic myocardium there seems to be no good reason to selectively limit carbohydrate intake in the CCU

In conclusion we have demonstrated widely *differing* practices in Coronary Care Unit diet therapy in the United States Caloric intake should be individualized and extremes such as overfeeding which may predispose the patient to angina or near-starvation diets which predispose to hypoglycemia are to be avoided The diet should eliminate items likely to cause *gastrointestinal* intolerance in specific patients and be comfortably modified in bulk ideally with multiple small feedings Both cholesterol and fat should probably be limited

Optimal salt intake will vary but for uncomplicated cases a no added salt diet seems reasonable Depending on circumstances, there may be benefit from increased or decreased dietary potassium

Metabolic needs of the infarction patient must be assessed daily supplemented by regular determinations of clinical status intake output serum glucose and electrolytes and by active consultation with the dietician Perhaps most important what is needed is more scientifically determined information about how dietary intake during acute myocardial infarction affects cardiac metabolism and the clinical course of the CCU patient

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Diet in the Coronary Care Unit*

Despite the fact that in 1970 a poll of 3 600 doctors revealed 90 per cent to favor some form of diet therapy for their CCU patients great confusion persists over what diet is best We surveyed over 290 major medical centers using a questionnaire and asked chief dieticians if doctors used a routine CCU diet for the first 24 to 72 hours of admission If the answer was negative they were asked to fill out the remainder of the questionnaire using the most common diet ordered in the setting of acute myocardial infarction No distinction was made between the first eight to twenty four hours (where admittedly many patients receive nothing by mouth as their condition is stabilized) and the remaining 48 to 60 hours of the acute phase of coronary care

Results

Seventy one per cent of the 290 institutions polled responded About 60 per cent of dieticians acknowledged the use of a routine CCU diet Caloric intake was evenly distributed across a wide range of choices less than 1 000 calories in 13 per cent of cases 1 000 to 2 000 calories in 8 5 per cent 1 200 to 1 400 in 20.5 per cent 1 400 to 1 600 in 16 per cent 1 600 to 2 000 in 20 per cent greater than 2 000 calories per day in 5 5 per cent and variable intake in 16 5 per cent Only about half of these diets were bland Most institutions clearly favor three meals per day (64 per cent) although significant numbers of patients (25 5 per cent) receive multiple small feedings or snacks While the majority of diets restrict cholesterol or saturated fat (65 per cent) roughly 22 per cent of these restrict cholesterol only Salt restriction in the form of a 2g Na diet was restricted in almost 50 per cent of cases although nearly 20 per cent of diets contain either no salt restriction or merely no added salt (about 4 Gm of sodium) Overwhelmingly CCU diets contain no potassium restriction About half reduce roughage either via low bulk foods or liquids and relatively few (10 per cent) restrict carbohydrates

From this data we may infer that no consensus exists regarding what to feed the CCU patient In fact very little is known about the advantages and liabilities of different diets

It has been shown that many myocardial infarction patients consume less than 200 calories a day in the CCU Such starvation diets may result in profound hypoglycemia a cause of increased cardiac work angina or myocardial necrosis On the other hand our data suggest that 40 per cent of hospitals feed their patients meals containing over 1 400 calories per day Add to this at least 200 calories from keep open" intravenous solutions of dextrose and water and it is apparent that many patients will arbitrarily be "overfed This may at least theoretically be attended by angina due to increased cardiac output with splanchnic dilatation Intuitively such problems might be lessened by the use of small frequent feedings although there has been no clinical study to support this

Similarly the bland diet which our data shows to have wide acceptance has not been proved to have any special physiologic merit In individual cases it may be prudent to restrict foods known to be tolerated poorly Similarly cardiac stimulants are perhaps best avoided since they may increase heart rate and myocardial oxygen consumption Hot and cold beverages however have been allowed with impunity without ill effects

Most CCU diets restrict fat and cholesterol presumably because of the myocardial depressant effects of free fatty acids and the well known association of lipids and coronary artery disease However it is curious that 22 per cent of diets contain restrictions in cholesterol only It has been shown that the blood level of cholesterol is more susceptible to influence by the quantity and quality of fat in the diet than by the amount of cholesterol in it Cholesterol absorption from the bowel is dependent upon dietary fat intake Therefore it does not make sense to restrict cholesterol without concurrently restricting dietary fat, especially saturated fat

How much salt should the CCU diet contain? Our question

*The opinions or assertions contained herein are those of the authors and are not to be construed as official or necessarily reflecting the views of the Medical Department of the Navy or the Naval Service at large

naire shows that roughly half the country favors the 2 Gm sodium diet This practice presumably derives from earlier data that demonstrated decreased renal blood flow in congestive heart failure with secondary retention of salt and water This degree of sodium restriction may be dangerous for many reasons, principally that in the presence of decreased cardiac output loss of extracellular sodium chloride may further decrease output An argument can also be made against unlimited salt intake since some Americans habitually consume l rge amounts of salt with their meals and the risk of fluid overload and congestive heart failure in the presence of acute myocardial infarction is real A reasonable compromise would appear to be a no added salt diet which in most hospitals contain 3 to 4 Gm of sodium with alterations made according to clinical status

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In conclu ion we have demonstrated widely differing practices in Coronary Care Unit diet therapy in the United States Calori intake should be indi idualized and extremes such as overfeeding which may predispose the patient to angina or near starvation diets which predispose to hypoglycemia are to be a oided The diet should eliminate items likely to cause gastrointestinal intolerance in specific patients and be comfortably modified in bulk ideally with multiple small feedings Both cholesterol and fat should probably be limited

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Letters to the Editor

Effect of vagus nerve stimulation on ventricular fibrillation threshold

To the Editor

We read with interest the article of Yoon and associates[1] Effects of vagal stimulation atropine and propranolol on fibrillation threshold of normal and ischemic ventricles in the January 1977 issue of AMERICAN HEART JOURNAL Their findings further confirm observations made in our own laboratory[2-4] to the effect that efferent vagal nerve stimulation (VNS) requires a background of augmented sympathetic tone in order to raise ventricular fibrillation threshold (VFT) We have noted as do Yoon and co workers that vagal effects on ventricular vulnerability are annulled by pretreatment with propranolol[2,3] This is also the case with vagal effects on ventricular excitability[5]

Yoon and associates conclusion that VNS raises VFT under control conditions while in agreement with the observations of Kent and colleagues[8] is at variance with our own findings which are that VNS has little or no effect on VFT in the absence of augmented sympathetic tone We employed a single pulse technique for VFT testing whereas Yoon and co workers employed a train of pulses technique It has been demonstrated that a train of closely spaced pulses delivered to the ventricles is a potent stimulus for local sympathetic neurohormonal release[9,10] We hypothesize that artifactual enhancement of sympathetic tone by the train of pulses technique explains the discrepancy between our results and those of Yoon and associates and Kent and colleagues The important unifying observation is that the effect of VNS on VFT is mediated indirectly through cancellation of the effects of efferent adrenergic tone Also the train of pulses technique may be unsuitable for VFT testing in circumstances in which a constant baseline level of sympathetic tone is desirable

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Reply

To the Editor

We appreciate the opportunity of responding to the letter of Dr Kolman and colleagues It is true that our findings confirm their observation that the effect of vagal stimulation on ventricular fibrillation threshold (VFT) is indirect and mediated through inhibition of the sympathetic activity They indicate that our observation that vagal stimulation increases VFT in nonischemic ventricles is at variance with their results but the two results in open chest dogs are quite similar They showed the mean increase in VFT of 26 per cent in 10 open chest dogs and we demonstrated the 35 per cent increase in eight open chest dogs They decentralized the left stellate ganglion and employed a single pulse technique for VFT testing while we left the stellate ganglia intact and used a train of rapid pulses for VFT determination It is possible that the level of underlying sympathetic tone was higher in our dogs and this resulted in a greater increase in VFT during vagal stimulation Their letter and our reply merely point out that the results of vagal stimulation on VFT can vary with different experimental techniques

We also studied the effect of vagal stimulation in the eight dogs during acute coronary occlusion and found that vagal stimulation has no effect on VFT in ischemic ventricles Myocardial ischemia produces marked depression in excitability and conductivity in the affected area leading to increased ventricular inhomogeneity and instability which facilitate ventricular arrhythmias We concluded that the potentially beneficial effect of vagal stimulation was not strong enough to counteract the deleterious effects of myocardial ischemia and failed to increase VFT In a recent clinical study continuous infusion of a vagotonic agent edrophonium hydrochloride failed to alter the over all incidence of ventricular arrhythmias in patients with acute myocardial infarction The frequency of ventricular premature beats was not significantly reduced and the appearance of ventricular tachyarrhythmias was not prevented by edrophonium infusion Therefore

evidence is not yet available to indicate that vagotonic agents are useful in the management of patients with ventricular arrhythmias during acute myocardial infarction

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Wolff Parkinson White (Type B) Ebstein s anomaly and congenital ichthyosis

To The Editor

I had the occasion to examine a 14 year-old white male with Wolff Parkinson White (Type B) Ebstein s anomaly and congenital ichthyosis A family tree for four generations was constructed

There are two siblings in his immediate family both are male and both have congenital ichthyosis The family physician in rural Kentucky reports neither have a cardiac murmur or a history of tachycardia Electrocardiograms of the two brothers read by the author are normal

A paternal uncle and the paternal grandmother also have this skin malady The same physician reports no cardiac abnormalities in these individuals Again I have read the grandmother s electrocardiogram and it is normal None could be obtained on the uncle

The other member of the family with congenital ichthyosis is a maternal great uncle The family knew of no cardiac problems in this individual but objective first hand evidence is unavailable

My review of the cardiology and dermatology literature did not reveal a previous observation of this triad

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Venture research

To the Editor

Your editorial in the December 1976 issue of AMERICAN HEART JOURNAL advocates revision of the present practice of allocating research grants While agreeing with most of the sentiments expressed in the article may I voice my disagreement on some points?

We all agree that the greatest asset of any country lies in the skills and talents of its people and it would serve the best interest of the country and of humanity if those possessing exceptional abilities, capable of original thought and holding the promise of great achievements were given every help and encouragement The question is how these people are to be found and what is the best way of helping and encouraging them

Unfortunately there is no known method of recognizing outstanding talent until its manifestation in outstanding achievement Bright young people more often shine by virtue of a retentive memory and personal charm than by original thought Conversely men who later reveal themselves as geniuses, often seem to have difficulties in communicating with their fellows Their work has often been overlooked and sometimes ridiculed by their contemporaries after its completion and publication how can it be expected that a small panel of critics would recognize its merits in its incipient stage?

Apart from the difficulty of finding the geniuses of the future the question still remains what is the best way of fostering their talents I *strongly disagree* with the opinion that society has to cross their palms with silver and pave their *path with gold* Surely a sense of mission the desire to leave the world a better place than they had found it and the necessity of answering the question—if to no one else then to themselves— *What have you* done with your talents? must be a stronger incentive than wanting a bigger automobile than their neighbor

Removing all obstacles and smoothing all paths does not seem to pay *in the case* of much lesser talents either or if it does, the law of diminishing returns nowhere operates with greater force than in this field Nowadays when anyone with a *modicum of talent* can receive free university education in most prosperous countries the recipients do not appreciate their good *fortune nearly* as much as we the older generation did to whom higher education was still an honor and privilege I am not advocating the other extreme Surmounting all obstacles *per ardua ad astra* demands a stronger character than most of us possess But removing all the *arduum* is a mistake People do *not appreciate* something that comes too easily or is indeed thrown at them

I am convinced that in *some cases* a surfeit of money is a positive disadvantage At least this was the impression I had in my nodding acquaintance with cancer research A sum of money will always find outlets if not usefully then wastefully Whenever I see six highly qualified authors to a not very

significant paper I cannot help wondering what their individual contributions were Was the last one the spelling expert? Or for instance are those innumerable congresses really necessary or just means of draining surplus funds?

In my opinion the most useful change in the present system of allocating funds for research would be to tie a *certain part* of the grant to achievement Human nature being as it is a judicious combination of the stick and the carrot is likely to *bring better results* than either an oversized stick or an oversized carrot by itself Granting agencies wield a miniature stick in that they can demand progress reports and withhold further allocations but they have no carrot to offer The grant is received by the grantee whether he makes a half hearted or a whole hearted effort and irrespective of the importance of his work I do of course realize that the object of a research grant is to make research possible hence it has to be paid out while the research is in progress but it also has the object of getting the best return for the outlay of large sums of money This end would be better served if the research workers were given some incentive to do their work quickly and efficiently At present the end of a research project at least to some of the participants may mean the end of a secure comfortable and undemanding period which they may want to continue as long as possible

An incentive could be provided by awarding minimal grants while a project is in progress with the promise of a merit award when it is finished This award could be made more for meritorious than for indifferent work One possible way of its administration could be the subsidizing of high ranking journals enabling them to pay their contributors at equal rates to popular press and publishers to pay authors whose work is too specialized to command large sales Another possibility would be to set prizes at a much less exalted level than the one in a million chance prizes like the Nobel prize

May I also comment on the recommendation of the Editorial of canalizing more effort into theoretical work than is done at present By a somewhat superficial analogy theorizing has often been compared with fitting pieces of a jigsaw puzzle together This may be apt in some fields of medical research it certainly does not apply to others Biochemistry for instance seems comparable to a tree with the skeleton clearly visible and the work of contemporary science is to follow it through to its branches and branchlets There seems no need for theories new research is largely a matter of finding new facts It is in such fields where twentieth century science has done truly magnificent work I remember reading an anecdote in the *Readers Digest* of a country doctor working in the early decades of this century to whom asking his patients for a sample of urine was an expedient for getting his tonic bottles back A good deal of distance seems to stand between his surgery and the Pathologic Laboratory of a modern hospital

Some pathologic phenomena like carcinogenesis or atherogenesis are still unexplained Experience shows that important prophylactic and therapeutic measures can be put in *practice* long before the causation of a disease is understood but in such cases research is of the nature of groping in the dark and progress can be agonizingly slow It is in these fields *where* there is a great need for scientists who are capable of fitting the jigsaw pieces together and bringing nearer an understanding of etiologic and pathogenetic factors

Here I believe the basic difficulty is that the common usage of the word research means only experimentation and data collecting irrespective of whether in that particular field there is a need for theorizing or not For instance when applicants for a research grant are asked for details of their research plan the description of the experiments they propose to carry out the animals they will use etc they are clearly given to understand that the granting authority uses the term research in this sense and the kind of application they expect to receive will be of the nature of The effect of dopamine on the intestinal circulation of Vitamin A deficient rats By not giving even a hint that they are willing to consider theorizing as research the authorities tend to perpetuate the present state with a disproportionate stress on experimentation and data collecting In other words while it is generally recognized that the experimenter and data collector has to eat while doing not immediately useful work it is apparently not recognized that the theoretician also has to do so Admittedly the theoretician does sedentary work and his caloric requirements are likely to be less than those of his physically more active fellows but it may be useful to point out that even he needs an occasional square meal

Disproportionate stress on data collecting and experimentation is somewhat reminiscent of a police force whose duties consist solely of taking fingerprints and picking up cigarette ends without anyone correlating information and drawing conclusions

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Potassium and salt substitutes

To the Editor

It is uncommon today to see a medical journal without some advertisements for generic names used as potassium supplements I would like to advocate an inexpensive source of potassium supplement usually unadvertised

Most of the available salt substitutes contain potassium chloride as the major ingredient One gram contains 11 to 1[illegible] mEq of potassium and a negligible *amount of sodium* (less than one mEq per 100 grams) *Some of these* salt substitutes are available in small packages 1/2 or one gram These small packages are an inexpensive *and convenient* source of potassium supplement in addition to the original use as a salt substitute

A few complications *have been reported* with the commonly used *potassium* supplements perhaps the use of a salt substitute as a potassium supplement would have no complication other than hyperkalemia

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Computerized electrocardiography

To the Editor

In the December 19/6 issue of AMERICAN HEART JOURNAL, (9? 773 780) Drs Burchell and Reed reported on A test experience with a machine processed electrocardiography diagnosis The recognition of "normal and some specific patterns Two serious errors appear in the article which require immediate correction (1) The title of the computer print-out p 778 states Sinai/Bonner ECG Analysis and (2) lines 2 and 3 of the summary on p 780 refer to commercially available *IBM* Bonner Mt Sinai System

Initially I did work at Mt Sinai Hospital in New York in conjunction with IBM and Dr Bonner s staff This effort was terminated in 1968 69 At present among the commercially available programs there is the IBM Bonner program as studied by Drs Burchell and Reed in this article and a distinctly different Mt Sinai Hospital/Cro Med Bionics Corporation system Since I hav personally studied many of the computer ECG programs available I do agree in principle with the findings of Burchell and Reed concerning the IBM Bonner ECG program as reported

For perspective a good review appeared in the September 19 6 issue of *The American Journal of Cardiology* (38 362 3/6) by Dr Cesar A Caceres A study of a detailed analysis of the performance of the Mt Sinai/Cro Med system in Brussels in over 23 000 cases was published by J Enderle and associates In a recently published book I have covered the current status of computerized electrocardiography

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Book reviews

Pre Excitation By M Irene Ferrer Mount Kisko New York 1976 Futura Publishing Company Price $27 50

Much has been written over the past few decades about the pre excitation state This reviewer wonders if so much concern over this one electrophysiologic state is justified It is intriguing and interesting and of great importance to the patient who has the syndrome and to the physician in charge who must contend with its many facets and complications But so much has been written on this subject that it would be almost impossible for someone to be thoroughly acquainted with the entire literature on this subject This is even evident in this monograph

The book describes the mechanisms associated ar rhythmias significance and management very well The illustrations are well selected and the legends are very good Readers should remember that the functional state and the influence of the time course of the order of activation of more than one wave front on the completed electrocardiogram are important as well as underlying myocardial disease The role and even existence of special tracts near the A V node needs careful consideration It is because of these important asso ciated factors that so much interest in the pre excitation syndrome has been created This is a very good book on an interesting electrophysiologic and clinical state in cardiol ogy

Physiological and Clinical Aspects of Cardiac Auscultation By Dr Alan Harris Dr George Sutton and Dr Malcolm Towers Philadelphia 1976 J B Lippincott Company 416 pages Price $48 00

This is an excellent book for all doctors especially medical students housestaff and all trainees in medicine The use of auscultation in medicine is a dying art even though it is most important for good clinical cardiology The contributors are excellent clinicians who have developed their respective contributions well The book correlates the findings by auscul tation with the hemodynamic clinical pathologic and echo cardiographic and other recordings very well The use of many illustrations excellent ones in color along with a brief well written text is most effective This is a highly recommended book

Neural Regulation of the Heart Edited by Walter C Randall Ph D New York 1977 Oxford University Press Price $21 95

This book emphasizes the role of the nervous system in cardiac regulation in the normal heart and its influence on abnormal cardiac states Interest in the influence of the nervous system on cardiac function commanded the attention of physiologists during the first part of this century In more recent years this interest was replaced by studies of hemody namic phenomena This change is interesting since it reflects the tendency to emphasize one aspect of cardiovascular physiology to the exclusion of another Any clinician and investigator knows that no aspect of cardiovascular phys ology can be ignored All aspects are important and enjoy an integrated role among all others This book edited by Randall summarizes selected aspects of the role of the nervous system in cardiac function The various contributors review studies and thoughts lucidly Because each contributor presents his isolated portion to the book the book fails to represent the characteristics of a monograph written by one author but represents more a series of papers which are somewhat disconnected from the others Regardless this is an extremely important subject in need of greater attention and study Randall's book should stimulate clinical and laboratory research in the subject of the nervous control of the heart and circulation Therefore this is a good and welcome publication which contains a great deal of useful information Critical study of the book can be rewarding to all physicians and physiologists interested in the heart and circulation The book is a good one worth owning for repeated study The anatomic and physiologic presentations are good and important

Cardiovascular Physiology Third Edition By Robert M Berne and Matthew N Levy Saint Louis 1977 The C V Mosby Company 282 pages Price $9 95

This is a brief and nicely written and well illustrated review of cardiovascular physiology The authors are physiologists with experience and interest in cardiovascular physiology who have been teaching the subject for many years The selected aspects of cardiovascular physiology described are important ones for learning cardiovascular physiology This book should interest clinicians as well as physiologists since the principles discussed are fundamental ones The material referred to in the bibliographies are mainly rather recent The classic publi cations of Frank Wilson Craib Wolferth and others are not even listed Lewis and Wilson have contributed extensively to electrocardiography and electrophysiology Yet their publica tions and those of others are not listed The same is true of the early and fundamental basic studies related to the cardiac pump Regardless this is an excellent review for students housestaff and physicians and serious investigators will find this to be a good start on important subjects of cardiova cular physiology It is obvious that the authors have designed the book for medical and graduate students as they indicate in their preface This teaching objective is well achieved It is highly recommended for them but it hoped that the next edition or printing will include references to the classics in cardiova cular physiology which should stimulate students to enter full time careers in physiology and academic medicine

Books received

Current Concepts in Radiology vol three Edited by E James Potchen M D St Louis 1977 The C V Mosby Company 42 pages Price $39 50

The Biochemistry of Smooth Muscles Edited by Newman L Stephens, M D Baltimore 1977 University Park Press 718 pages Price $34.50

A Diagnostic Approach to Chest Diseases 2nd edition Differential Diagnoses Based on Roentgenographic Patterns By Glen A Lillington and Robert W Jamplis Baltimore 1977 The Williams & Wilkins Company 591 pages Price $54 00

Beta adrenergic Blockers and Hypertension Edited by D Ganten R Dietz B Lüth and F Gross, Stuttgart Germany 1976 Georg Thieme Verlag 201 pages

Recent Advances in Blood Coagulation Edited by Leon Poller New York 1977 Churchill Livingstone 377 pages. Price $35 00

Low Density Lipoproteins Edited by Charles E Day and Robert S Levy New York 1977 Plenum Publishing Corporation 433 pages Price $39.50

Refresher course in cardiac imaging

A refresher course in cardiac imaging will be presented by the North American Society for Cardiac Radiology March 20 through 24 1978 at the MGM Grand Hotel Las Vegas Nevada

The program will follow the standard format of morning lecture series followed by afternoon workshops Faculty members of internationally known authorities in cardiology radiology ultrasound nuclear medicine and computerized tomography will direct the program The course is sponsored by the American College of Radiology and the council on Clinical Cardiology of the American Heart Association and will offer approximately 23 hours of credit for Category I of the AMA Physician s Recognition Award

For further program content information please contact Dr Richard B Jaffe telephone (801) 328 9061 ext 225 or write Teri Dibble Conferences and Institutes Division of Continuing Education University of Utah 1152 Annex Building Salt Lake City Utah 84112

Workshop in Echocardiography

A Workshop in Echocardiography will be held at the Newporter Inn Newport Beach California on January 25 through 28 1978 The workshop will be directed by Louis Evan Teichholz M D Associate Chief of Cardiology Mount Sinai Medical Center and Associate Professor of Medicine Mount Sinai School of Medicine New York For further information regarding this workshop please contact Ms Billie N Chiles Tampa Tracings P O Box 1245 Tarpon Springs Fla 33589

Fifth International Congress on Electrocardiology

The Fifth International Congress on Electrocardiology will be held in Glasgow Scotland on September 5 through 8 1978 There will be sessions on Programmed Electrocardiography (Pacing Studies) Cardiac Electrophysiology Mathematical Modelling Dynamic Electrocardiography ECG Criteria Exercise Electrocardiography and Computer Studies in Electrocardiography Full details of the Congress can be obtained from the Congress Secretariat University Department of Medical Cardiology Royal Infirmary Glasgow G4 OSF Scotland

Optical microscopy and photomicrography in the biomedical sciences

The Marine Biological Laboratory Woods Hole Massachusetts announces Optical Microscopy and Photomicrography in the biomedical sciences a residential laboratory course March 12 18 1978 This concentrated program is intended primarily for scientists and physicians who require theoretically based training and experience in modern light microscopy Among the topics to be discussed and practiced will be bright and dark field phase and modulation contrast high extinction polarized light and differential interference microscopy fluorescence and color and black and white photomicrography and cinemicrography The Instructor in Chief will be Robert Day Allen of Dartmouth College Additional information and application materials may be obtained from the Director of Admissions Marine Biological Laboratory Woods Hole Mass 02543 phone 617 548 3705

Intra aortic balloon pump symposium

Daniel Freeman Memorial Hospital Inglewood (Los Angeles) California presents A Symposium on Clinical and Technical Application of the Intra Aortic Balloon Pump on March 10 11 1978 at the Pacifica Hotel in Culver City California

Up to fifteen hours of Formal (Category 1) credit towards the California Medical Association Certificate in Continuing Medical Education and the American Medical Association Physician s Recognition Award may be reported State of California Provider No 00075R N allows ten contact hours of Continuing Nursing Education Fee for physicians $100 00 Fee for R N $75 00

For further information please contact Valerie Grace R N Department of Education Daniel Freeman Memorial Hospital 333 North Prairie Avenue Inglewood California 90301 Telephone (213) 674 7050 extension 111

Information for authors

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Editorial

Can death from venous thromboembolism be prevented in elderly patients with hip fractures?

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To enable elderly patients with hip fractures to walk again as soon as possible after their injury stabilization of the fracture by a pinning operation or replacement of the femoral head is commonly undertaken. Among the benefits claimed for early operation and walking is the avoidance of those complications which are attributed to prolonged bed rest—muscle wasting osteoporosis hypostatic pneumonia and bedsores. While early mobilization could theoretically help to reduce the frequency of venous thromboembolism in practice pulmonary embolism remains a serious problem and kills approximately one out of every ten patients within three months of their injury. Pulmonary embolism however can be prevented in these very high risk patients. This was demonstrated convincingly in 1959 by the clinicopathological study of Sevitt and Gallagher in which treatment with an oral anticoagulant markedly reduced the frequency of venous thrombosis and eliminated the risk of fatal pulmonary embolism. The efficacy of prophylactic anticoagulation in preventing pulmonary embolism has been reaffirmed on many occasions but it has become clear that the reduction in overall mortality which can be achieved by oral anticoagulation is not as great as was originally suggested because diseases other than venous thromboembolism kill many of these elderly and infirm patients[2]

Despite its proven efficacy in preventing death from pulmonary embolism prophylactic anticoagulation is unpopular. In 1973 a survey of antithrombotic practices in orthopedic surgery in the U S A suggested that only 11 per cent of surgeons used prophylactic anticoagulation routinely in the management of elderly patients with hip fractures while a further 36 per cent offered treatment to selected patients. More recently in a similar survey in the United Kingdom we found that only 3 per cent of orthopedic surgeons routinely used prophylactic anticoagulation in patients with hip fractures. If they are not using anticoagulants have orthopedic surgeons discovered a more convenient and equally effective alternative form of prophylaxis?

As judged by the surveys[3] about one third of orthopedic surgeons in the U S A and about a half of their British colleagues offer no prophylactic treatment whatsoever and small groups of surgeons in both countries use dextran aspirin combinations of dextran and aspirin and low dose heparin on a prophylactic basis. Those who use dextran can quote studies which support the value of this agent but scrutiny of the literature concerning prophylaxis with dextran in hip fracture patients and in general surgical patients reveals an amazing lack of consistency. Evidence can be marshalled to support four viewpoints—that dextran prevents venous thrombo

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sis[6] that it does not prevent venous thrombosis[7] that it prevents pulmonary embolism,[8] and that it does not prevent pulmonary embolism[9] Trials of poor design variations in the dose and types of dextran used and differing trial endpoints have undoubtedly led to confusion about this agent and there is clearly a need to evaluate it once and for all in an adequately controlled trial using mortality from pulmonary embolism as a firm endpoint Aspirin too, has proved disappointing in preventing venous thrombosis in groups of patients at lesser risk than those with hip fractures[10] Zekert and colleagues,[11] however, claimed that prophylactic treatment with aspirin prevented both venous thrombosis and fatal pulmonary embolism in these patients, but their results lack confirmation In our own studies of venous thromboembolism in elderly patients with hip fractures we found no evidence to indicate that agents which modify platelet behavior (dipyridamole dipyridamole plus aspirin, and flurbiprofen) could influence the frequency of isotopically diagnosed venous thrombosis We also failed to confirm that low dose heparin can prevent venous thrombosis in patients with hip fractures[12] It seems to us unlikely that lengthy studies of these agents using mortality as an endpoint, can be justified

Thus at present oral anticoagulation is the only regime which has been proved to prevent venous thrombosis and pulmonary embolism in elderly patients with hip fractures To those surgeons who offer prophylactic anticoagulation to previously fit patients with hip fractures whose premature death from pulmonary embolism would be untimely we would say that they are acting in accordance with the evidence available, to those who offer alternative forms of prophylaxis we would urge them to critically appraise the conflicting evidence so far available while to those who offer no prophylaxis at all we would remind them that they are allowing a number of pulmonary embolic deaths to occur in patients who could otherwise have survived to live an independent and useful life

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Clinical communications

Intrapulmonary acetylcholine in bilharzial cor pulmonale

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Intrapulmonary infusion of acetylcholine dilates the small pulmonary arterioles and decreases the pulmonary arterial pressure as it traverses the lung it is completely inactivated and so it has no effect on the systemic blood pressure or heart rate[1] Bishop and associates[2] found that infusion of acetylcholine in the pulmonary artery of patients with mitral stenosis produced a small fall in the mean pulmonary artery pressure and a negligible fall in the mean arterial oxygen tension without any change in the alveolar oxygen tension

In a healthy subject breathing room air the small difference between the alveolar and arterial oxygen tensions (A a difference) is due to the normally occurring small right to left shunting and uneven distribution of the pulmonary blood flow relative to alveolar ventilation The A a difference also depends on the diffusing capacity of the alveolo capillary membrane The diffusion component is extremely small in normal subjects breathing room air and is nullified by breathing oxygen enriched mixtures Such high oxygen mixtures also correct the ventilation component of the ventilation perfusion imbalance Thus at high levels of alveolar oxygen any A a oxygen difference is almost entirely due to anatomical right to left shunts

Bilharzial cor pulmonale is a chronic vascular cor pulmonale due to widespread affection of the small pulmonary arteries Zaki and colleagues[5-7] were of the opinion that in this disease besides the systolic overloading of the right ventricle there is also a diastolic overload the latter is due to various vascular shunts namely intrasplenic porto pulmonary bronchopulmonary and pulmonary arteriovenous Although these shunts were demonstrated yet they were not quantitated Some of these shunts can explain arterial hypoxemia met with in some patients with bilharzial cor pulmonale

The aim of this work is a further study of the mechanisms of pulmonary hypertension in bilharzial cor pulmonale and the arterial hypoxemia found in some patients with this disease

Material and methods

Fifteen male bilharzial patients with clinical radiological and electrocardiographic evidence of cor pulmonale were studied Their ages ranged between 11 and 47 years All had bilharzial hepatic fibrosis and splenomegaly None had any episode of gastro oesophageal bleeding Five had ascites (Nos 2 4 8 11 and 12) All had a hemoglobin level above 75 per cent and were free of respiratory diseases

Conventional right heart catheterization was performed and pressures at different sites of the right side of the heart and the pulmonary circuit were obtained All pressures were measured with the zero point 5 cm below the sternal angle in the supine position The cardiac output was calculated according to the Fick principle and the pulmonary vascular resistance was derived In three patients in whom the pulmonary artery pressure was normal at rest (Nos 2 7 and 8) an exercise test was performed to prove the presence of early cor pulmonale

Ten mg of acetylcholine diluted in 10 ml saline

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Table I Hemodynamics in bilharzial cor pulmonale

Patient no	Age	Mean P A P* (mm Hg) Resting	After exercise	After A C	P C P	Resting C O (Litres /min)	Resting P V R (units)
1	16	77		60	5	7 00	8 30
2	47	12	21		8	12 55†	9 45
3	36	48		45	9	4 80	11 30
4	35	34		27	7	10 30†	2 80
5	32	63		63	8	5 28	11 70
6	40	43		44	10	5 40	6 40
7	15	9	19	–	10	6 80	1 50
8	40	7	20		9	11 40†	0 56
9	28	61		62	8	5 90	8 30
10	35	73		73	8	5 78	10 60
11	15	54		54	6	4 70	11 06
12	11	35		35	10	8 2[illegible]	3 70
13	20	36		35	8	5 90	5 70
14	24	53		52	9	6 71	7 00
15	25	40		26	8	8 [illegible]0	8 20

Abbreviations P A P = Pulmonary artery pressure C O = Cardiac output P V R = Pulmonary vascular resistance A C = Acetylcholine P C P = Precapillary wedge pressure
†The high cardiac output in patients Nos 2 4 and 8 can be due to the hyperkinetic circulation and hypervolemia frequently met with in patients with advanced bilharzial liver fibrosis and ascites

were infused into the pulmonary artery via the cardiac catheter over a period of ten minutes, i e at a rate of one mg /minute In patients Nos 3, 9 and 15 only 5 mg of acetylcholine were infused at the same rate i e , during five minutes Arterial blood samples were taken via an indwelling arterial needle before at the middle and at the end of the infusion i e , after the infusion of 5 or 10 mg of acetylcholine Arterial samples were taken repeatedly after the end of the infusion for a period of six to ten minutes The per cent oxygen saturation of the blood samples was determined by oximetry The pulmonary artery pressure was determined before and at the end of infusion The heart rate and the systemic arterial blood pressure were also followed all through the experiment and the chest was auscultated for evidence of bronchospasm during and after acetylcholine infusion In all patients receiving 10 mg acetylcholine except patient No 1 the whole procedure was repeated while the patients were breathing 100 per cent oxygen The oxygen inhalation was maintained via an oxygen mask for five minutes before and all through the acetylcholine experiment

The acetylcholine experiment was also performed on four healthy normal control subjects but to avoid catheterization of healthy subjects 10 mg of the drug were infused via the antecubital vein

Results

The pertinent hemodynamic data are listed in Table I The pulmonary artery pressure was elevated in all the patients except Nos 2 7, and 8 in whom it was normal at rest but showed an abnormal increase after exercise, and who were considered as early cor pulmonale patients These three patients were included in the study before catheterization because of positive clinical radiological, and electrocardiographic signs of cor pulmonale The per cent oxygen saturation of the arterial blood at rest while breathing room air ranged between 94 5 and 99 in all the patients except patient No 4, who had 89 5 per cent saturation (Table II) After breathing 100 per cent oxygen the arterial oxygen saturation ranged between 97 per cent and 100 per cent in all the patients including patient No 4 who had arterial desaturation while breathing room air (Table III)

Acetylcholine experiment The effects of acetylcholine on arterial oxygen saturation while the patients were breathing room air are shown in Table II Fig 1 shows the average effects of the infusion of 10 mg acetylcholine in three patients with early cor pulmonale in 12 patients with moderate to severe cor pulmonale, and in four normal subjects The figure also shows the average results of the infusion of only 5 mg acetylcholine in three patients In all the patients there was an evident drop in arterial oxygen saturation after the infusion of 5 mg acetylcholine and the drop was more evident as the infusion continued to 10 mg The drop persisted for about two minutes after the end of the infusion and gradually improved during the following eight minutes but did not reach the pre infusion level In eleven of the patients who had intrapulmonary injection of 10 mg acetylcholine the experiment was repeated while they were breathing 100 per cent oxygen (Table III) In five patients there was no change in arterial oxygen saturation in four patients there was a drop of 1 per cent and in the remaining two patients (Nos 7 & 14) the saturation dropped from 98 5 and 97 per cent respectively, before infusion to 94 per cent for both of them after infusion

Table II Arterial oxygen saturation while breathing room air at rest before and at the end of 5 and 10 mg Acetylcholine infusion and every two minutes thereafter

No	Before A C	5 mg A C	10 mg A C	2 min after	4 min after	6 min after	8 min after	10 min after
Patients								
1	97.0	95.5	94.0	95.0	95.0	96.5	95.0	
2	96.5	87.0	85.5	84.5	86.5	87.0	87.0	
3	95.5	97.0		97.0	86.5		88.0	
4	89.5	88.0	86.5	87.0	86.5	86.5	86.5	88.0
5	94.5	90.0	88.0	87.0				91.0
6	95.0	89.5	87.0	88.5		89.5	93.0	95.0
7	96.5	9 .5	90.5	91.5	90.5	90.0	89.5	88.0
8	94.5	89.0	84.0	8 .0	89.0	90.0	90.0	97.0
9	95.0	93.0		91.5	91.5			
10	94.5	90.0	96.5	94.0		94.0		
11	95.0	88.0	84.0	86.0				
12	97.0	94.0	96.0			98.5		
13	95.0	97.0	93.5	94.5		94.5		
14	96.0	89.5	86.5					91.0
15	95.5	91.0		97.5	92.5			
Normals								
1	95.0	93.0	95.0		94.0			
2	99.5	9 .0	99.5		98.0			
3	98.0	93.5	96.5		98.5			
4	99.5	98.0	94.5					

A C = Acetylcholine

In the normal subjects breathing room air the arterial oxygen saturation showed a mild reduction during and after acetylcholine infusion via the antecubital vein the average reduction was 3 per cent only (Fig 1) While breathing 100 per cent oxygen acetylcholine did not change the arterial oxygen saturation in any of the normal subjects

Discussion

Bilharzial cor pulmonary is primarily due to widespread affection of small pulmonary arteries by obliterative changes Many workers from Alexandria explained the pathologic physiology of this disease Badawi and co workers[3] are of the opinion that the whole picture in bilharzial cor pulmonale can be explained by fixed widespread obliterative arteritis affecting the small pulmonary arteries Zaki and co workers[4] on the other hand believe that besides this important factor various shunts at different levels as well as hypervolemia contribute to the hemodynamics of the disease They stressed the role of protosystemic and porto pulmonary venous shunts as well as

Table III Arterial oxygen saturation while breathing room air and 100 per cent oxygen before and after acetylcholine

Patient no	Oxygen per cent at room air	Oxygen per cent during oxygen inhalation	
		Before acetylcholine	After acetylcholine
2	98.5	99.5	98.5
4	89.5	90.5	99.5
5	94.5	100.0	100.0
6	95.0	98.5	98.5
7	96.5	99.5	94.0
8	94.5	99.5	99.5
10	94.5	100.0	100.0
11	95.0	99.0	99.0
12	97.0	99.0	98.0
13	95.0	98.5	97.5
14	96.0	97.0	94.0

bronchopulmonary shunts in the pathogenesis of the diseases Porto pulmonary venous shunts and pulmonary arteriovenous shunts were blamed by these authors for the arterial oxygen desaturation which they encountered in some patients with bilharzial cor pulmonale

In the present work the arterial oxygen saturation at rest ranged between 94.5 per cent and 97 per cent except in patient No 4 in whom it was 89.5 per cent his resting mean pulmonary artery pressure was 34 mm Hg and he had marked ascites The ventilatory disturbances associated with marked ascites can contribute to his arterial undersaturation In fact his arterial oxygyen saturation was completely corrected after oxygen inhalation (Table III) It is also interesting to note that acetylcholine infusion in this patient produced a mild but appreciable lowering of his pulmonary artery pressure indicating that a vasoactive component probably due to hypoxia was contributing to his pulmonary hypertension

Acetylcholine has a dilating effect on the pulmonary arteries and capillaries The results of this dilating effect are not normally very obvious The action of any dilating drug will become more obvious if the vessel to which it is applied has previously been constricted[4] These results are more obvious in pathological pulmonary hypertension in the presence of active vasoconstriction In bilharzial cor pulmonale the pulmonary hypertension is essentially due to organic obliter

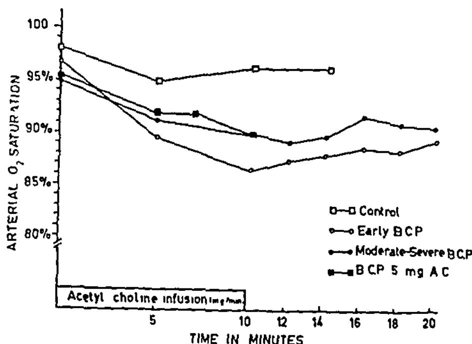


Fig 1 Average changes in arterial oxygen saturation after intravenous infusion of 10 mg acetylcholine in four normal subjects (control) and the intrapulmonary infusion of 5 mg (three patients) or 10 mg (12 patients) with bilharzial cor pulmonale *(BCP)* (three patients with early and nine with moderate to severe BCP)

ative arteritis and our previous experience with acetylcholine[5] failed to show any effect of this drug even on the post exercise elevation of the pulmonary artery pressure In the present study we could also not detect any effect of acetyl choline infusion on the levels of the pulmonary artery pressures except in three patients Nos 1 4 and 15 In these patients there was a mild reduction in the pulmonary artery pressure after acetylcholine infusion which denotes the presence of a vasospastic element Hypoxia can be a factor only in patient No 4 an active stage of arteritis can explain the spasm in all the three patients De Faria and associates[9] demonstrated a vasospastic factor in their patients with bilharzial cor pulmonale

In all patients studied, there was a reduction in the arterial oxygen saturation by intrapulmonary acetylcholine infusion This reduction without lowering of the pulmonary artery pressure indicated that the action of acetylcholine in bilharzial cor pulmonale was distal to the small pulmonary arteries, i e, in the territories of rich precapillary and capillary anastomosis in the vicinity of the alveoli and distal air passages Tarabeih[10] found reduced compliance and increased work of breathing in bilharzial cor pulmonale while Abdel Rassoul[11] demonstrated in his series uneven ventilation These ventilatory disturbances and the obliterative changes in the pulmonary arteries are mainly focal and disturb the ventilation/perfusion ratio This defect will become more manifest if it is further disturbed by dilatation of the vessels supplying hypoventilated alveoli Furthermore, intrapulmonary injection of acetylcholine can lead to narrowing of the distal respiratory passages with hypoventilation of their corresponding alveoli thus accentuating the disturbed ventilation/perfusion ratio However auscultation of the patients during and after acetylcholine infusion failed to reveal evidence of bronchospasm, but this does not rule out spasm of distal bronchial passages The fact that arterial oxygen undersaturation after acetylcholine was completely corrected by 100 per cent oxygen inhalation indicates that hypoventilation was the main factor in the production of arterial hypoxemia It is thus logical to assume that the mechanism of arterial oxygen undersaturation after acetylcholine in our patients was related to selective opening up of vessels supplying underventilated segments of the lungs The same explanation has been suggested for similar results in pulmonary hypertension due to mitral stenosis[3,8,12] (Soderholm and Werko 1959 Harris 1961 and Bishop et al 1962)

We can deduce that the arterial oxygen desaturation which occurs in some patients with bilharzial cor pulmonale results from a disturbed ventilation/perfusion ratio The fact that oxygen

inhalation corrected the arterial desaturation in patient No 4 and prevented the occurrence of arterial desaturation in all the patients except two after acetylcholine infusion confirms this suggestion Porto pulmonary shunts were considered important in the production of arterial oxygen desaturation in bilharzial cor pulmonale[7] The oxygen saturation of portal blood is relatively high and averages 78 per cent and therefore porto pulmonary shunts cannot produce appreciable arterial desaturation unless the venous admixture is great furthermore it should not be completely corrected by oxygen inhalation Patients Nos 7 and 14 had arterial oxygen saturation of 96 5 and 96 per cent respectively at rest Acetylcholine infusion while breathing room air diminished the saturation to 88 and 86 5 per cent respectively Acetylcholine infusion while breathing 100 per cent oxygen decreased their arterial oxygen saturation only to 94 per cent Thus 100 per cent oxygen appreciably corrected the desaturation after acethylcholine The correction can be explained by improving the ventilation/perfusion ratio These patients apparently had also veno arterial shunts which were encouraged by acetylcholine and their effect could not be nullified by oxygen inhalation the shunts however were modest and lowered the arterial oxygen saturation only to 94 per cent

Fig 1 shows that the effect of acetylcholine infusion in normal subjects were not marked as in bilharzial cor pulmonale All the figures for the per cent oxygen saturation after acetylcholine in the normal subjects were still within or just below the normal range (Table II) In these subjects acetylcholine was infused slowly via the antecubital vein and it is expected that during its passage from the arm to the lungs part of the drug was deactivated by the choline esterase normally persent in the blood

Conclusion

The pulmonary hypertension in bilharzial cor pulmonale is mostly obliterative and fixed Intra pulmonary acetylcholine does not decrease the pulmonary hypertension except when a factor of vasospasm is present Arterial oxygen desaturation is not a feature of bilharzial cor pulmonale and when present it is mild This oxygen desaturation is predominantly the result of disturbed ventilation/perfusion ratio Anatomical veno arterial shunts play only a minor role

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Cardiac reserve during isoproterenol stress in patients with aortic valve disease before and after corrective surgery

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In a recent report Bailey and associates[1] emphasized that survival after aortic valve replacement in patients with aortic regurgitation depends upon the extent of left ventricular hypertrophy Bolooki and Kaiser showed that preoperative cardiac function is one of the important determinants of early postoperative survival in patients with aortic valve disease and severe hypertrophy However a close relation between left ventricular hypertrophy and function has not been defined previously[3, 4] Further it is questionable to which extent different types of overload can influence myocardial contractility[5] Since hypertrophy compensates an increased cardiac stress we believe that the investigation of cardiac reserve is best suited to study the relation between cardiac hypertrophy and ventricular function Studies investigating reserve force of the hypertrophied heart muscle are scarce indeed Bolen and colleagues[6] found a deterioration of cardiac function during afterload stress in seven patients with severe aortic regurgitation two of which however had associated coronary artery disease Lee and co workers[7] reported a reduced function during exercise in severe aortic stenosis but not in moderate stenosis A relation between left ventricular muscle mass and reserve force was not established in these studies

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The purpose of the present study was to quantitate left ventricular function at rest and during isoproterenol infusion in patients with aortic valve disease and to correlate the reserve force of the left ventricle with the degree of left ventricular hypertrophy

Methods

1 Patients Preoperative studies were performed in 35 patients undergoing right and left heart catheterization for diagnosis and evaluation of valvular heart disease There were ten females and 25 males Each patient gave informed consent for the conduction of the study No patients received premedication before catheterization The patients with aortic valve lesions represent a consecutive nonselected series

The control group consists of nine patients without evidence of valvular or myocardial heart disease They all had normal coronaroangiograms The mean age in this group was 47 3 years (range 36 to 58 years)

Twelve patients with predominant aortic stenosis had a mean age of 43 4 years (range 14 to 59 years) Average aortic valve area was 0 68 cm²/M² (range 0 40 to 1 29 cm²/M²) and average peak systolic pressure gradient was 78 3 mm Hg (range 40 to 120 mm Hg) Aortic root angiography was performed in all these patients and revealed additional aortic incompetence in eight patients estimated as 1+ (out of a maximum of 3+) No patients had additional mitral valve disease The presence and severity of symptoms were assessed from the clinical records We recorded NYHA functional class considering

typical symptoms associated with aortic valve disease angina syncope and dyspnea Seven patients of this group were in Class II four in Class III and one in Class IV Selective coronaro angiography was performed in all patients except the child of 14 years and showed coronary arteries without obstructions

Twelve patients had predominant aortic regurgitation Their mean age was 38 years (range 16 to 63 years) All patients had massive regurgitation scored as 3+ from aortic root angiography Average aortic valve area in this group was 2 19 cm²/M² (range 1 41 to 2 9 cm /M²) Six patients had additional peak systolic pressure gradients between 6 and 20 mm Hg Two patients had additional mild mitral incompetence without mitral stenosis Five patients were in Class II and seven in Class III In the six patients above 40 years of age coronary angiography showed no abnormalities

Two patients had mixed aortic valve lesions with massive aortic regurgitation of 3+ aortic valve areas of 1 15 and 1 25 cm /M² and peak systolic pressure gradients of 48 and 50 mm Hg Additional mild mitral incompetence was present in one patient Both patients were in Class III and had coronary arteries without obstructions

Pre and postoperative studies were performed in another series of six patients Four of them had preoperatively predominant aortic stenosis with an average aortic valve area of 0 58 cm²/M² (range 0 42 to 0 70 cm²/M) and a peak systolic pressure gradient of 116 mm Hg (range 64 to 186 mm Hg) Mild additional (1+ out of a maximum of 3+) aortic regurgitation was found in two of these four patients The remaining two patients had a massive aortic regurgitation of 3+ with aortic valve areas of 1 7 and 2 3 cm²/M² and peak systolic pressure gradients of 12 and 30 mm Hg The postoperative evaluation was carried out 9 2 ± 3 3 months (mean ± SEM) after aortic valve replacement (Bjork Shiley prosthesis)

2 Conduction of the study Heart rate left atrial pressure left ventricular pressure (8F Brockenbrough catheter transseptal approach) and aortic pressure (8F pigtail catheter femoral artery) were recorded before use of contrast material using Statham P23Db pressure transducers at the midchest position Thereafter 50 ml Urografin 76 were injected into the left ventricle using the Brockenbrough catheter while cineangiograms were exposed at 48 frames/sec on

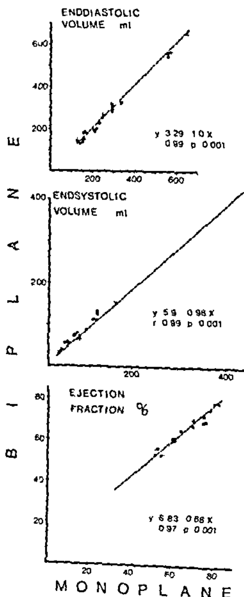


Fig 1 Comparison between end-diastolic volume end systolic volume and ejection fraction measured by single plane (monoplane) and biplane angiography r = correlation coefficient

a 35 mm film (RAO position) Simultaneously the ECG and the aortic pressure were recorded with a paper speed of 100 mm /sec on an oscillomink direct writing system Ventriculography was repeated after a waiting period of at least 25 minutes during continuous infusion of 0 3 μg/Kg body weight/min isoproterenol The Brockenbrough catheter was withdrawn into the left atrium and ventriculography was performed by injection into the atrium Thereafter selective cinecoronarography was performed using the Judkins technique

Table I Comparison of cardiac function before and during isoproterenol infusion between patients with predominant aortic stenosis and patients with predominant aortic regurgitation (both groups had comparable degrees of ventricular hypertrophy)

	LVMMI	*HR (beats /min)*	*LVSP (mm Hg)*	*AoPd (mm Hg)*	*EDV (ml /M²)*	*EF (%)*	*VCF (circumfer /sec)*	*MLAP (mm Hg)*	*LVEDP (mm Hg)*	*AVA (cm²/M²)*
Rest										
Aortic stenosis	226 5	81 0	196 4	71 5	127 9	63 4	1 05	14 4	20 6	0 68
(n = 11)	±80 7	±11 7	±30 3	±15 2	±67 7	±16 3	±0 40	±9 0	±10 0	±0 26
Aortic regurgitation	223 5	79 5	155 3	61 3	171 8	58 8	0 94	11 0	17 9	2 19
(n = 8)	±67 6	±12 6	±15 4	±14 6	±34 7	±12 8	±0 23	±5 2	±6 4	±0 40
P value	n s	n.s	<0 01	n s	n s	n s	n s	n.s	n s	<0 001
Isoproterenol										
Aortic stenosis	226 5	130 9	254 0	66 0	118 6	68 9	1 72	16 0	18 8	0 44
(n = 11)	+80 7	±13 6	±49 2	±15 2	±77 9	±16 3	±0 62	±11 5	±13 9	±0 31
Aortic regurgitation	223 5	122 9	174 5	57 0	151 8	70 5	1 81	9 2	9 9	2 63
(n = 8)	±67 6	±23 6	±18 1	±14 3	±38 5	±10 6	±0 40	±7 3	± 5 1	±1.20
P value	n s	n s	<0 001	n s	n s	n s	n s	n s	n s	<0 01

Abbreviations LVMMI = left ventricular muscle mass index (Gm /M of body surface area) HR = heart rate LVSP = left ventricular systolic pressure AoPd = diastolic aortic pressure EDV = end-diastolic volume EF = ejection fraction VCF = mean fiber shortening rate MLAP = mean left atrial pressure LVEDP = left ventricular end diastolic pressure AVA = aortic valve area

Data are mean values ± standard deviation

3 Angiographic methods Quantitative ventriculography was done using a sphere calibration technique and the area length method[7] modified for the RAO position[8,11] End diastolic and end systolic volumes were derived from the largest and smallest silhouettes of the left ventricle using the apex and the aortic root as reference points Ventriculographic images selected for analysis were taken from the first four sinus beats following contrast material injection Heart rate did not change more than 5 b p m during ventriculography as compared to heart rate measured during pressure recordings All volume data were corrected according to the formula of Sandler and Dodge[8] To assess ventricular function, ejection fraction was determined as stroke volume divided by end diastolic volume times 100 per cent The minor equator (D) was calculated as D = 4 area/ $\pi \times$ L where L is the long axis of the ventricle The percentage shortening of minor equator was determined as end diastolic minus end systolic divided by end diastolic equator Mean circumferential fiber shortening rate was calculated as percentage shortening of minor equator divided by ejection time as measured from the aortic pulse during ventriculography Ventricular volumes were determined by single plane as well as biplane ventriculography in 25 patients in order to compare both methods Left ventricular wall thickness was measured in the RAO projection as proposed by Falsetti and colleagues[1] Left ventricular mass was determined according to Rackley and associates[13] Aortic valve area was calculated utilizing a modification of the Gorlin formula[14] after Bache and co workers[15] aortic valve area = Q/ 37 8 $\sqrt{}$ PPSG + 10 where Q = cardiac output divided by the systolic ejection period $PPSG$ = peak to peak left ventricular to aortic pressure gradient Cardiac output was calculated as angiographic stroke volume times heart rate Valve areas determined by this method were found to be greater than those reported by others using the Fick principle[16,17] but agree closely with values obtained by Lewis and colleagues[18] and by Kennedy[1] using the angiographic technique We believe that this method is preferable because even in "pure aortic stenosis we found frequently mild regurgitation during aortic root angiography Statistical analysis was carried out using the Student t test and linear regression analysis

Results

Comparison of monoplane and biplane volumes for normal and enlarged ventricles showed an excellent correlation (r = 0 994) for end diastolic volumes ranging from 134 to 645 ml (Fig 1) A similar correlation (r = 0 996) was found for end

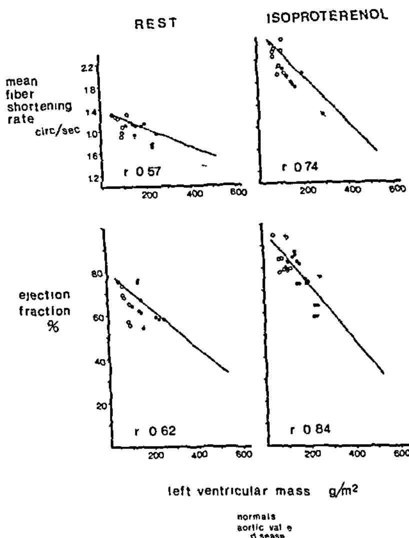


Fig. 2. Correlation between left ventricular muscle mass and mean fiber shortening rate *(upper panel)* or ejection fraction *(lower panel)* during rest *(left)* and during isoproterenol infusion *(right)*. r = correlation coefficient. *The open circles* represent values of normal patients, *closed circles* represent values for patients with aortic valve disease.

systolic volumes over the range of 26 to 425 ml and for ejection fractions ($r = 0.973$) over a range of 34 to 84 per cent.

Eleven out of twelve patients with predominant aortic stenosis and 8 out of 12 patients with predominant aortic regurgitation were selected according to their left ventricular mass to achieve two groups with nearly identical and therefore comparable degree of hypertrophy (Table I). Left ventricular peak systolic pressure and aortic valve area were significantly different between both groups ($p < 0.01$). Heart rate, diastolic aortic pressure, end diastolic volume, ejection fraction, mean fiber shortening rate, mean left atrial pressure, and left ventricular end diastolic pressure were not significantly different ($p > 0.05$) between both groups either at rest or during isoproterenol infusion.

It is therefore justified to correlate the ejection fraction and mean fiber shortening rate to the left ventricular muscle mass irrespective of the type of overload as shown in Fig. 2. During rest the correlation for mean fiber shortening rate was poor ($r = 0.57$, $p < 0.001$) but improved during isoproterenol ($r = 0.74$, $p < 0.001$). Both these regression lines are significantly different ($p < 0.01$). The relation between muscle mass and ejection fraction was poor at rest ($r = 0.62$, $p < 0.001$) but also improved considerably during isoproterenol ($r = 0.84$, $p < 0.001$).

Table II Left ventricular function in normal patients and in patients before and after aortic valve replacement under resting conditions and during isoproterenol stress

	LVMMI *‡	*HR (beats /min)*	*LVSP (mm Hg)*	*AoPd (mm Hg)*	*EDV (ml /M²)*	*EF (%)*	*VCF (circumfer /sec)*	*MLAP (mm Hg)*	*LVEDP (mm Hg)*	*AVA (cm /M²)*
Rest										
Normals (n = 9)	87.3 ±22.6†	72.0 ±10.2	125.8 ±11.3	71.6 ±9.3	91.9 ±26.9	68.1 ±7.9	1.19 ±0.18	9.1 ±2.8	10.4 ±4.5	1.68 ±0.46
Before aortic valve replacement (n = 6)	315.6 ±62.1	80.3 ±11.0	188.7 ±56.9	55.0 ±6.2	223.0 ±71.7	48.0 ±15.9	0.63 ±0.27	25.3 ±11.7	29.3 ±9.9	1.0[illegible] ±0.[illegible]9
Before vs Normals	<0.001	n.s	<0.05	<0.01	<0.01	<0.05	<0.001	<0.05	<0.01	n.s
After aortic valve replacement (n = 6)	146.9 ±43.5	77.6 ±8.2	143.3 ±13.3	74.5 ±8.2	95.7 ±14.7	68.3 ±11.2	1.29 ±0.39	8.8 ±3.5	13.2 ±1.7	1.30 ±0.31
After vs Before	<0.01	n.s	n.s	<0.01	<0.01	<0.05	<0.05	<0.05	<0.01	n.s
After vs Normals	<0.05	n.s	<0.05	n.s	n.s	n.s	n.s	n.s	n.s	n.s
Isoproterenol										
Normals (N = 9)	87.3 ±22.6	142.0 ±11.9	128.8 ±16.1	67.6 ±9.4	74.1 ±21.2	85.0 ±5.4	2.43 ±0.10	4.2 ±1.3	6.1 ±2.9	2.3[illegible] ±0.48
After aortic valve replacement (n = 6)	146.9 ±43.5	144.8 ±6.1	183.3 ±12.2	62.0 ±6.5	92.2 ±18.5	76.5 ±6.9	2.03 ±0.24	9.8 ±4.7	9.3 ±5.0	1.20 ±0.36
After vs Normals	<0.05	n.s	<0.001	n.s	n.s	<0.05	<0.01	<0.05	n.s	<0.001

Abbreviations as in Table I
†Data are mean values ± standard deviation
‡Left ventricular muscle mass index (LVMMI) measured in Gm /M² of body surface area

A poor but significant ($r = 0.47$, $p < 0.01$) inverse relation was found between left ventricular end diastolic pressure and ejection fraction at rest. This correlation however worsened during isoproterenol infusion ($r = 0.44$, $p < 0.05$). A similar inverse relation between mean left atrial pressure and ejection fraction was observed at rest ($r = 0.56$, $p < 0.001$) and improved during isoproterenol ($r = 0.66$, $p < 0.001$), suggesting that mean left atrial pressure roughly reflects pump function of the left ventricle in aortic valve disease.

Table II shows the results in patients before and nine months after aortic valve replacement as compared to the control group. Left ventricular muscle mass, which was significantly elevated before surgery ($p < 0.001$), decreased after valve replacement ($p < 0.01$ if sets of paired observations were compared) but remained abnormally elevated ($p < 0.05$). Resting values of ejection fraction, mean fiber shortening rate, and mean left atrial pressure which were pathologic before surgery normalized after valve replacement. Cardiac reserve tested during isoproterenol infusion after surgery revealed an abnormal response of ejection fraction, mean fiber shortening rate and mean left atrial pressure as compared to normal patients ($p < 0.05$). Fig 3 indicates that the persisting hypertrophy after corrective surgery is associated with an incomplete restoration of cardiac reserve, suggesting that the relation between mass and reserve remains valid after surgery.

Discussion

Some methological problems need discussion. First of all it has to be considered that monoplane angiography may result in erroneous measurements of left ventricular volumes. Cohn and colleagues[1] found good agreement of monoplane

and biplane angiography in normal patients and in patients with coronary artery disease without evidence of asynergy. Our observation was that monoplane and biplane angiograms correlate excellently in ventricles with aortic valve disease without coronary artery disease (Fig. 1). This is mainly due to the fact that ventricular geometry in aortic valve disease remains nearly normal. The ejection fraction and the mean circumferential fiber shortening rate[30] were used in this study to define left ventricular function at rest and during isoproterenol stress. Peterson and coworkers[7] compared isovolumic and ejection phase indices in normal and diseased hearts and found that in patients with diffuse myocardial involvement ejection phase contractile indices offer a preferable mode for assessing myocardial function. The ejection phase indices showed superior sensitivity for identifying normal and abnormal patients with minimal individual overlap whereas isovolumic indices although separating normal and diseased hearts showed considerable overlap of individual values. The ejection fraction measured at rest has prognostic significance in the surgical treatment of valvular heart disease since patients with depressed ejection fractions have a poorer short term prognosis than patient with normal ejection fractions.[3] It was further shown that the evaluation of the contractile reserve determined by the ejection fraction after postextrasystolic potentiation or during epinephrine infusion helped to establish a close relation between ventricular function and prognosis in patients with coronary artery disease.[33]

Isoproterenol as a beta stimulating drug enhances left ventricular performance in normal and diseased hearts.[1, 2] Quinones and colleagues described an augmentation of contractility as measured from an increase of mean circumferential fiber shortening rate of 58 per cent during isoproterenol infusion in normal individuals. Geha and associates found a significant increase of contractile behavior in normal and hypertrophied dog hearts. In the present study we used isoproterenol to evaluate cardiac reserve.

Left ventricular function and reserve were not different between chronic pressure and chronic volume overload if patients with nearly identical left ventricular muscle masses are compared. Mehmel and coworkers using a similar approach found no differences of Vpm between two groups of patients with chronic pressure and volume

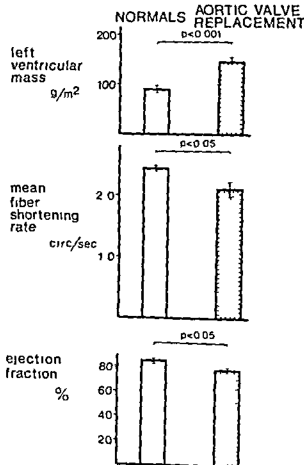


Fig. 3. Left ventricular muscle mass and reserve function in normal patients and in patients after aortic valve replacement. Left ventricular muscle mass is still significantly increased nine months after surgery. Reserve function (mean fiber shortening rate and ejection fraction) is reduced in these hypertrophied hearts. The columns represent mean values ± SEM.

overload but with comparable muscle masses. They concluded that in advanced hypertrophy contractility is reduced irrespective of the stimulating factor. Our results support this concept. Therefore we related left ventricular function to the degree of hypertrophy irrespective of the type of aortic valve lesion. Under control conditions this relation was poor probably due to the compensatory capacity of the hypertrophied ventricle[2] and the Frank Starling mechanism.[25] When however the hypertrophied hearts were forced to mobilize their reserve a close inverse relationship between muscle mass and reserve force was found (Fig. 2). Thus stress could demonstrate a depression of cardiac reserve when

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Rest										
Normals	87 3	72 0	125 8	71 6	91 9	68 1	1 19	9 1	10 4	1 68
(n = 9)	±22 6†	±10 2	±11 3	±9 3	±26 9	±7 9	±0 18	±2 8	±4 5	±0 46
Before aortic valve	315 6	80 3	188 7	55 0	223 0	48 0	0 63	25 3	29 3	1 0
replacement (n = 6)	±62 1	±11 0	±56 9	±6 2	±71 7	±15 9	±0 27	±11 7	±9 9	±0 9
Before vs Normals	<0 001	n s	<0 05	<0 01	<0 01	<0 05	<0 001	<0 05	<0 01	n s
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After vs Before	<0 01	n s	n s	<0 01	<0 01	<0 05	<0 05	<0 05	<0 01	n s
After vs Normals	<0 05	n s	<0 05	n s	n s	n s	n s	n s	n s	n s
Isoproterenol										
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After vs Normals	<0 05	n s	<0 001	n s	n s	<0 05	<0 01	<0 05	n s	<0 001

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differences at rest were only slight or absent This suggests that changes in the development of hypertrophy occur which may be responsible for the loss of contractile reserve in these hearts Spann and colleagues[6] found in hypertrophied isolated cat papillary muscles that hypertrophy in the absence of cardiac failure was associated with a depression of contractility per unit of myocardium Gunning and associates[7] concluded from experiments in hypertrophied cat papillary muscles due to pressure overload that the depressed contractility is associated with an augmented myocardial oxygen consumption Strauer and Tauchert[28] found an inefficient energy utilization in the isolated hypertrophied human ventricular myocardium These results point out that biochemical correlates at the cellular level may be involved in the process leading to mechanical dysfunction in advanced cardiac hypertrophy A second mechanism may be responsible for the decline of contractile reserve with increasing severity of hypertrophy Marchetti and colleagues[29] described a reduced coronary reserve in dogs with moderate hyper trophy due to volume overload This suggests that myocardial perfusion may also be respon sible for the impairment of contractile reserve in hypertrophied hearts

Comparison of pre and postoperative evalua tion in six patients with advanced aortic valve disease and severe left ventricular hypertrophy shows a drastic reduction of left ventricular muscle mass after surgery to 53 per cent of the preoperative value This regression, however is incomplete if compared to normal patients An incomplete regression of left ventricular hyper trophy was also observed by Kennedy and co workers[35] in patients with homograft aortic valve replacement and by Papadimitriou and asso ciates[36] in dogs after closure of a large aortocaval fistula Cardiac function at rest which was severely compromised before surgery, normalized completely in our patients after successful correc tion of overload contractile reserve however was still depressed This demonstrates that after correction of overload by aortic valve replace ment the hearts shifted upwards and to the left on the mass function curve shown in Fig 2 indicating improved cardiac performance It has to be considered however, that Bjork Shiley prostheses produce an increased afterload which may be responsible for the incomplete regression of left ventricular hypertrophy and the incom plete restoration of contractile reserve

Summary

The relations between left ventricular (LV) hypertrophy as estimated by LV mass and LV function and between LV hypertrophy and cardiac reserve were evaluated in 26 patients with aortic valve disease and in nine normal patients who served as controls Ejection fraction (EF) and mean circumferential fiber shortening rate (VCF) served as indices of LV function Reserve force of the left ventricle was tested by ventricu lography during infusion of 0 3 μg/Kg body weight/min isoproterenol EF and VCF were not significantly different ($p > 0.05$) either at rest or during isoproterenol infusion if patients with aortic stenosis were compared to patients with aortic regurgitation having comparable LV masses Therefore we correlated the EF and VCF to the LV mass of all patients irrespective of the type of aortic valve lesion Poor but significant inverse correlations were found at rest between LV mass and EF ($r = 0.62$) and between LV mass and VCF ($r = 0.57$) These correlations improved considerably during isoproterenol $r = 0.84$ for EF and $r = 0.74$ for VCF

LV function was evaluated in another six patients with aortic valve disease before and nine months after successful aortic valve replacement by Bjork Shiley prostheses LV mass before surgery was 3 6 times control and decreased after surgery to 1 7 times control ($p < 0.01$) which is still significantly elevated ($p < 0.05$) EF and VCF which were depressed before surgery ($p < 0.05$ $p < 0.001$) normalized after surgery ($p > 0.05$) but were reduced during isoproterenol infusion if compared to controls ($p < 0.05$) Thus stress ventriculography in aortic valve disease could demonstrate a linear decrease of cardiac reserve with increasing severity of hypertrophy when resting function was normal or depressed only slightly Regression of hypertrophy was incomplete 9 months after correction of overload and LV function which was depressed before surgery normalized at rest but was impaired during stress suggesting that cardiac reserve was not fully restored

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but one case. Again these 14 patients were classified into one group.

It became apparent from the study of the clinical and pathological findings that the clinical features and hemodynamic alterations in each group were determined mainly by the function of the tricuspid valve, as will be described later. In addition, given the fact that most patients with Ebstein's anomaly probably have some degree of tricuspid malfunction, each of the three groups was termed as Tricuspid Stenosis Dominant Type, Tricuspid Insufficiency Dominant Type, and Mild Type, respectively.

1. Tricuspid Stenosis Dominant Type (cases No. 1 to 8, Table I)

Clinical features. The most consistent symptoms in this group were exertional dyspnea and palpitation, which were observed in five patients (cases No. 2, 3, 4, 7, and 8). Bouts of paroxysmal tachycardia were present in two (cases No. 1 and 8) and hypoxic spells in two (cases No. 2 and 5). Three patients showed severe cyanosis and five showed moderate cyanosis.

Radiology. A typical radiologic cardiac silhouette described as being box like or balloon shaped with a narrow pedicle was present in four patients (cases No. 2, 3, 4, and 8). This contour was formed mostly by the enlarged right atrium which caused the bulging right border and ballooning of the right ventricular outflow tract which formed the protrusion of the left upper border. Cardiomegaly was present in all but one patient and the enlargement was estimated to be mild in four and moderate in three. Pulmonary vascularity was judged to be decreased in all.

Right heart catheterization. This study was performed on seven patients (Table IV). The right atrial A wave ranged from 6 to 11 mm Hg and the V wave ranged 6 to 10 mm Hg. The right ventricular systolic pressure ranged from 19 to 35 mm Hg and the end diastolic pressure ranged from 4 to 10 mm Hg. Five patients had a significant diastolic pressure gradient across the tricuspid valve. A right to left shunt at the atrial level was noted in five patients, two of these being demonstrated as having a left to right shunt also, and one of them had a ventricular septal defect (case No. 7).

Angiocardiography. This study was performed on seven patients and adequate films were obtained in all. In all patients the proximal chamber (the atrialized right ventricle) situated

Table I. Clinical findings in patients of Tricuspid Stenosis Dominant Type

Case No	Age (yr)	Sex	NYHA class	Cyanosis	CTR (per cent)	Double ball sign	Surgery	Autopsy
1	1	M	III	+++	61	+	palliative	–
2	7	F	III	+++	65	+	TVR	–
3	8	F	II	++	61	+	TVR	–
4	12	M	III	++	70	+	–	–
5	14	M	III	++	66	?	palliative	+
6	15	F	II	++	64	+	TVR	+
7	22	F	III	++	63	+	TVR	+
8	31	F	III	+++	70	+	TVR	–

CTR = cardiothoracic ratio; TVR = tricuspid valvular replacement; = unknown.

between the right atrium and the distal chamber (the functioning right ventricle) was confirmed as being present. In four patients contraction of the proximal chamber at the same time as the ventricular systole was noted, but in three patients (cases No. 1, 2, and 4) this chamber showed little contraction. The proximal chamber could be distinguished from the distal chamber by the notch toward the cardiac apex indicating the displaced attachment of the tricuspid valve (Fig. 1)[5] or by the different concentrations of the contrast medium in these two chambers (Fig. 3). In two patients (cases No. 1 and 6) in which the contrast medium was injected into the distal chamber, the proximal chamber surrounded by the parachute like deformed tricuspid valve was not opacified and this portion appeared as a shadow defect in the right ventricle like an intraventricular tumor (Fig. 2).

At peak diastole the superior aspect of the infundibulum rose above the superior aspect of the pulmonary trunk and this phenomenon became manifest in the frontal view as a ball like density within another round density area. This sign was initially termed as a "double ball sign" by Elliot and Hartmann and was noted in all patients of the Tricuspid Stenosis Dominant Type.

Anatomical findings. Detailed anatomical findings were obtained in 4 patients (cases No. 1, 5, 6, and 7). In these the anomaly was not simply a downward displacement of the attachment of the tricuspid valve but it was also an abnormality of the entire tricuspid valvular apparatus and of the architecture of the right ventricle. In

Clinical classification of Ebstein's anomaly

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Since the first description by Ebstein in 1866[1] several hundred cases have been reported and the anomaly has attracted much attention through its broad clinical spectrum

In this anomaly there is a variety of symptoms ranging from severe cyanosis congestive heart failure and death in infancy to no cyanosis in patients who lived till the age of 79 years without any symptoms In most previous studies however, these patients have been classified simply into severe or mild cases according to their clinical features In 1971 Bialostozky and colleagues[1] reported a review of 65 cases, and classified the patients into four groups according to their clinical findings and course

The purpose of this paper is to present three types of classifications of 26 patients with Ebstein's anomaly according to their clinical features, radiologic findings hemodynamic data and anatomical findings which were observed on surgery or autopsy and to consider the hemodynamic alterations in each type

Materials and methods

The 26 patients (12 males and 14 females) ranged in age from one to 51 years Routine chest x ray films were obtained in all patients Right heart catheterization and selective angiocardiography were performed in 24 patients Surgery was performed in 11 patients and autopsies were done in six patients of which five were postoperative

The diagnoses of the other 14 patients were confirmed by clinical findings and angiocardiography

Clinical classification

In four out of 9 patients in whom the detailed anatomical findings were obtained the tricuspid leaflets showed a great degree of deformity and the small tricuspid orifice was observed (cases No 1, 5 6 and 7) These patients were in a functional capacity Class II or III of NYHA, and they showed a moderate to severe cyanosis and a cardiomegaly The cardiomegaly was estimated to be mild (cardiothoracic ratio greater than 56 per cent) or moderate (cardiothoracic ratio greater than 66 per cent) except for one patient who showed a normal sized heart In two patients right heart catheterization revealed a pressure gradient across the tricuspid valve and in three patients the double ball sign[4] on angiocardiography was present The clinical findings of the four other patients (cases No 2 3 4 and 8) were judged to be similar to these four patients and therefore these eight patients were grouped together

All the patients with severe cardiomegaly (cardiothoracic ratio greater than 76 per cent) showed a mild to moderate cyanosis (cases No 9 to 12) In three patients in whom right heart catheterization was performed a tall and wide V wave of the right atrium was noted and on angiocardiography the double ball sign was present An incompetent tricuspid valve was found in three patients at surgery or autopsy These four patients were thought to resemble each other

Of the remaining 14 patients 11 were acyanotic and three showed mild cyanosis and all of them were in functional Class I or II The chest roentgenogram revealed a mild to moderate cardiomegaly and the double ball sign was absent in all

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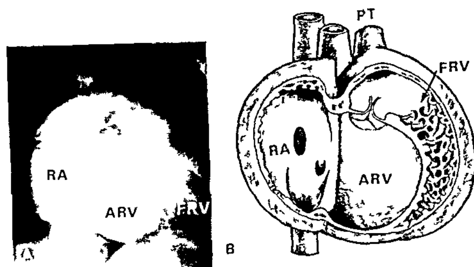


Fig 3 Frontal angiocardiogram in ventricular systole *(A)* and anatomical findings *(B)* of the patient of the Tricuspid Stenosis Dominant Type (case No 7) *RA* = right atrium *ARV* = atrialized right ventricle (proximal chamber) *FRV* = functioning right ventricle (distal chamber) *PT* = pulmonary trunk

The size of the distal chamber in three patients (cases No 5 6 and 7) was less than that of the definitive right ventricle in a normal person The right atrium was mildly enlarged and the eustachian valve had a tendency to be prominent in all patients One patient (case No 7) had a ventricular septal defect

2 Tricuspid Insufficiency Dominant Type (cases No 9 to 12 Table II)

Clinical features Two patients (cases No 9 and 10) were in Functional Class I and one patient (case No 11) showed a long stable course with only mild exertional dyspnea despite the marked ly enlarged heart Case No 12 was a 51 year old woman in whom cardiomegaly was first noted in her childhood and she remained asymptomatic until she had frequent bouts of tachycardia occurring at age 23 By the age of 41 she was first detected to be cyanotic and to have a severe cardiomegaly of 83 per cent The patient died from congestive heart failure at age 51 Cyanosis was found to be mild in three cases and moderate in one

Radiology Box like severe cardiomegaly was observed in all patients (Fig 4) One patient (case No 10) showed a rapid progress of cardiomegaly from 74 to 84 per cent during the two years prior to surgery On the other hand in two patients (cases No 11 and 12) the cardiomegaly remained unchanged for a long time Pulmonary vascularity was considered to be normal in all patients

Table II Clinical findings in patients of Tricuspid Insufficiency Dominant Type

Case no	*Age (yr)*	*Sex*	*NYHA class*	*Cyanosis*	*CTR (per cent)*	*Double ball sign*	*Surgery*	*Autopsy*
9	7	M	I	+	81	+	TVR	+
10	8	M	I	+	83	+	TVR	–
11	29	M	II	+	77	+	–	–
12	51	F	III	++	93	?	–	+

CTR = cardiothoracic ratio TVR = tricuspid valvular replacement
? = unknown.

Right heart catheterization (Table IV) The most characteristic finding was the presence of a giant V wave of the right atrium which indicated severe tricuspid insufficiency ranging from 11 to 17 mm Hg The right atrial mean pressure was equal to that of the right ventricle in two patients (cases No 9 and 10) The right atrial A wave ranged from 5 to 12 mm Hg and the right ventricular end diastolic pressure from 8 to 10 mm Hg A diastolic pressure gradient across the tricuspid valve was noted in one patient

Angiocardiography This study was performed on three patients The proximal chamber could not be distinguished in two (cases No 9 and 10) because of the absence of the notch indicating the displaced attachment of the tricuspid valve In one patient (case No 11) the proximal chamber was distinguished from the distal chamber by the

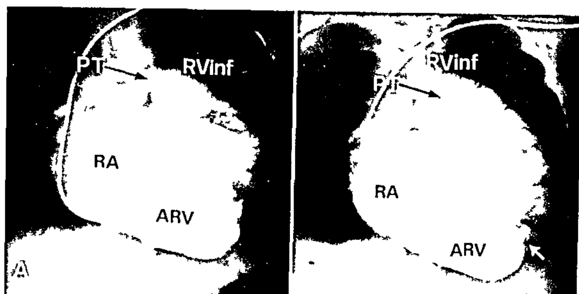


Fig 1 Frontal angiocardiogram of the patient of the Tricuspid Stenosis Dominant Type (case No 2) in ventricular systole *(A)* and in diastole *(B)* Arrow indicates the demarcating notch The double ball sign is shown in *(B)* *RA* = right atrium *ARV* = atrialized right ventricle (proximal chamber) *RV inf* = right ventricular infundibulum *PT* = pulmonary trunk

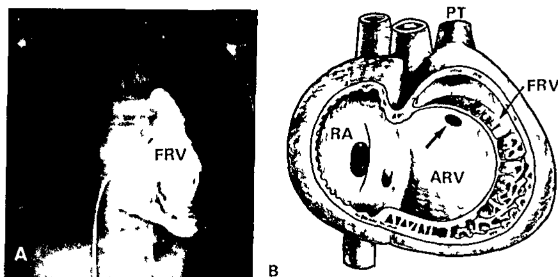


Fig 2 Frontal angiocardiogram in ventricular systole *(A)* and anatomical findings *(B)* of the patient of the Tricuspid Stenosis Dominant Type (case No 6) The atrialized right ventricle appears as a shadow defect in the right ventricle *Arrow* depicts a small opening in the parachute like deformed tricuspid valve *FRV* = functioning right ventricle (distal chamber) *RA* = right atrium *ARV* = atrialized right ventricle (proximal chamber) *PT* = pulmonary trunk

one patient (case No 1) the base of the anterior leaflet was completely anchored on the original right atrioventricular orifice and in the other three patients the entire attachment of the three leaflets was displaced downward into the right ventricle However the tricuspid valve remained anchored on the pars membranacea in all of the patients [3]

In three patients (cases No 1 5 and 6) the three leaflets were fused to each other to form a parachute with a small opening measuring 8 to 10 mm in diameter In one of them (case No 6) the parachute was connected to the inner surface of the wall of the right ventricle by numerous tiny tendinous fibers (Fig 2) In another patient (case No 5) the attachment of the tricuspid valve was deviated so far that the leaflets were just below the pulmonary valve resulting in the distal chamber consisting of only a small conus In case No 7 the attachment of the three cusps extended downward to the narrow ring formed by the crista supraventricularis parietal band and the abnormally developed crista septomarginalis (Fig 3)

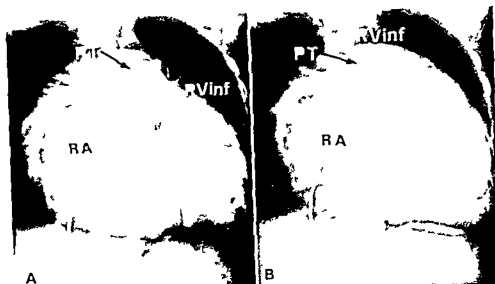


Fig 5 Frontal angiocardiogram in ventricular systole *(A)* and in diastole *(B)* of the patient of the Tricuspid Insufficiency Dominant Type (case No 10) *The right atrium and the right ventricle are markedly enlarged* The superior aspect of the right ventricular infundibulum rises above the superior aspect of the pulmonary trunk in *diastole and this appears in (B)* as a dense opaque ball within a ball ("double ball sign") *RA* = right atrium *RVinf* = right ventricular infundibulum

Discussion

It is generally accepted that the fundamental hemodynamic alterations in Ebstein's anomaly lie in the proximal chamber [9] The proximal chamber distends during the atrial contraction and reduces the amount of blood reaching the distal chamber and during the ventricular systole it contracts and forces the blood back into the right atrium Thus filling of the right ventricle is impaired and the pulmonary flow is reduced and cyanosis is produced by the right to left shunt through the atrial septal defect

These hemodynamic alterations were observed by angiocardiography in the patients reported here The proximal chamber was noted in 20 patients and this portion contracted at the same time as the distal chamber in 17 patients but in three patients of the Tricuspid Stenosis Dominant Type little contraction was shown It was of interest that even in the asymptomatic and acyanotic patients a large amount of blood was forced back into the right atrium by the contraction of the proximal chamber There was no significant difference in the size of the proximal chamber between the severe patients of the Tricuspid Stenosis Dominant Type and the patients of the Mild Type

It is thought that the hemodynamic alterations of the patients with Ebstein's anomaly have a

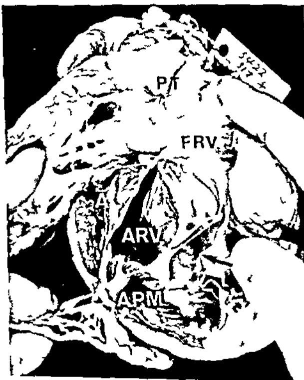


Fig 6 Specimen of the opened heart of the patient of the Tricuspid Insufficiency Dominant Type (case No 12) viewed from the right ventricular outflow tract Arrow indicates the large defect on the posterior and septal leaflet *AL* = anterior leaflet *APM* = anterior papillary muscle *ARV* = atrialized right ventricle (proximal chamber) *FRV* = functioning right ventricle (distal chamber) *PT* = pulmonary trunk



Fıg 4 Frontal chest roentgenogram of the patıent of the Trıcuspıd Insufficıencv Domınant Type (case No 9) demon stratıng box lıke severe cardıomegaly

dıfferent densıty of the contrast medıum Marked dılatatıon of the rıght atrıum and the rıght ventrıcle was observed ın all patıents The double ball sıgn was demonstrated ın all and the volume change of the ınfundıbulum was very large (Fıg 5)

Anatomıcal findıngs Anatomıcal findıngs were obtaıned ın three patıents In two patıents (cases No 9 and 10) each of the three leaflets was ıdentıfiable and showed a marked atrophy and ın case No 12 a large defect ın the septal and posterıor leaflet was found (Fıg 6) It appeared obvıous that there was severe trıcuspıd ınsufficıency ın these patıents

The anterıor leaflet arose from the normal orıfice ın all cases There was a marked dılatatıon of the rıght atrıum and of the dıstal portıon of the rıght ventrıcle An atrıal septal defect was present ın two patıents (cases No 9 and 10)

3 Mıld Type (cases No 13 to 26 Table III)

Clınıcal features Symptoms were present ın eıght of 14 patıents of thıs type and were mıld ın all The most common symptoms were exertıonal dyspnea present ın sıx patıents (cases No 13 15 17, 19 24 and 26) Bouts of paroxysmal tachycardıa occurred ın four and easy fatıgabılıty of precordıal paın was noted ın two (cases No 24 and 25) Mıld congestıve heart faılure was noted ın one patıent (case No 13) ın whom a large left to rıght shunt at the atrıal level was detected Nıne patıents were ın Functıonal Class I and the remaınıng five were ın Class II

Eleven patıents had no cyanosıs and of these five had no symptoms at all Cyanosıs was mıld ın three other patıents Hypoxıc spells or squattıng were not noted ın any of the patıents

Radıology Cardıomegaly was present ın all except one case Seven patıents showed a mıld cardıomegaly and sıx showed a moderate one A box lıke heart was present ın four patıents (cases No 14 17 21, and 26) Pulmonary vascularıty was consıdered to be normal ın all but one (case No 13) ın whom ıt was ıncreased

Rıght heart catheterızatıon (Table IV) Thıs study was performed ın all patıents of thıs type The rıght atrıal A wave ranged from 4 to 13 mm Hg, the V wave ranged from 6 to 17 mm Hg the rıght ventrıcular systolıc pressure ranged from 20 to 34 mm Hg and the end dıastolıc pressure of the rıght ventrıcle ranged from 2 to 13 mm Hg A dıastolıc pressure gradıent across the trıcuspıd valve was demonstrated ın two patıents The left to rıght shunt was detected ın three patıents and the rıght to left shunt ın one patıent

Angıocardıography Detaıled findıngs were obtaıned ın all of the patıents of thıs type The proxımal chamber was dıstınguıshed clearly ın 12 patıents and ın all of these patıents ıt showed a good contractıon ın accordance wıth that of the dıstal chamber The large anterıor leaflet was shown as a cocavo convex movement ın three patıents (cases No 16 17 and 19 Fıg 7) The double ball sıgn was absent ın all but one (case No 14)

Anatomıcal findıngs In two patıents surgery was performed and anatomıcal findıngs were obtaıned In case No 13 each of the three leaflets of the trıcuspıd valve was ıdentıfied wıth the large anterıor leaflet arısıng from the orıgınal atrıoventrıcular orıfice No trıcuspıd stenosıs was observed and no ınsufficıency was demonstrated by the normal salıne ınjectıon ınto the dıstal chamber durıng surgery In case No 10 the septal and posterıor leaflets were atrophıed and the large anterıor leaflet whıch was attached to the orıgınal orıfice seemed to compensate for the valvular functıon of the atrophıed two leaflets In these anatomıcal findıngs the archıtecture of the rıght ventrıcle was almost normal Atrıal septal defect was found ın two patıents

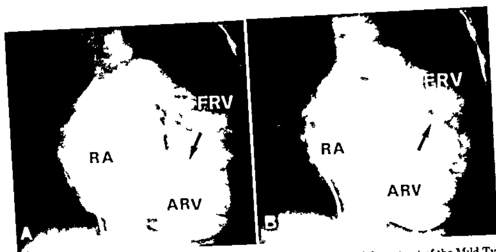


Fig 7 Frontal angiocardiogram in ventricular systole *(A)* and in diastole *(B)* of the patient of the Mild Type (case No 17) *Arrow* indicates the concavo convex movement of the large anterior leaflet of the tricuspid valve The double ball sign is not observable *RA* = right atrium *ARV* = atrialized ri ht ventricle (proximal chamber) *FRV* = functioning right ventricle (distal chamber)

an adequate sized distal chamber a sufficient output from the right ventricle should be main tained in spite of the presence of the proximal chamber One patient of the Mild Type (case No 13) had congestive heart failure and it was thought to be due to the large left to right shunt This was deduced from the disappearance of cardiac failure following the closure of the atrial septal defect This patient might be an excep tional example of the Mild Type because the large left to right shunt is rare in Ebstein s anomaly

The wide spectrum in Ebstein s anomaly to gether with the lack of longer follow up studies has resulted in a few reports about its natural history Makous and Vander Veer[9] estimated the life expectancy of Ebstein s anomaly to be 37 years from 219 cases reported throughout the world including six cases of their own By contrast Kumar and associates estimated median survival period to be 13 years from the 55 patients of his study This marked difference seems to be attributed to the fact that in Kumar and colleagues study many cases under one year of age were included Concerning natural death by Ebstein s anomaly Watson stated in an inter national co operative study of 505 cases that after an initially high mortality rate of 45 7 per cent from congestive heart failure during the first year of life the mortality settles to an average of 12 4 per cent which is scattered fairly uniformly throughout childhood and adolescence

According to Bialostzky and collegues classifi cation Group I was comprised of asymptomatic patients Group II of symptomatic patients with no progression of clinical indexes Group III of patients with marked symptoms as well as steady deterioration and Group IV of severely disabled patients It is likely that the patients classified as Mild Type in this report correspond to patients of their Group I or II and that the patients of the Tricuspid Stenosis Dominant Type and the Tricuspid Insufficiency Dominant Type would be included in their Group III or IV

The development of congestive heart failure and increasing cyanosis are grave prognostic signs The prognosis of the patients of the Tricuspid Stenosis Dominant Type is thought to be poor due to their grave clinical features and the oldest patient of this series showed severe cyanosis and exercise limitation at age 26

In patients of the Tricuspid Insufficiency Dominant Type congestive heart failure may develop especially in a patient such as case No 9 in whom cardiomegaly increased rapidly in a short time However care must be taken with this type because there are a number of patients with significant cardiac enlargement and a long stable course as in case No 11 Case No 12 seems likely to be an exaggerated example of this type She showed mild symptoms till age 40 even though there was severe cardiomegaly

It would be interesting to know the prognosis of the patients of the Mild Type In studying several reports of other investigators it is apparent that patients in class I or II of NYHA are most common[3] and even in this study cases of the

Table III Clinical findings in patients of Mild Type

Case no	Age (yr)	Sex	NYHA class	Cyanosis	CTR (per cent)	Double ball sign	Surgery	Autopsy
13	3	F	II	–	70	–	ASD clos	–
14	4	F	I	–	71	+	–	–
15	7	F	II	+	72	–	–	–
16	7	F	I	–	58	–	–	–
17	8	M	II	+	72	–	TVR	+
18	9	M	I	–	72	–	–	–
19	9	M	II	+	70	–	–	–
20	12	F	I	–	60	–	–	–
21	13	M	I	–	61	–	–	–
22	16	F	I	–	63	–	–	–
23	16	F	I	–	52	–	–	–
24	21	F	I	–	59	–	–	–
25	21	M	I	–	60	–	–	–
26	23	M	II	–	65	–	–	–

CTR = cardiothoracic ratio TVR = tricuspid valvular replacement
ASD clos = closure of the atrial septal defect

Table IV Right heart catheterization findings

Case No	Pressure in mm Hg						
	RA			RV			Diastolic pressure gradient across the tricuspid valve
	A wave	V wave	Mean	Systolic	End diastolic	Mean	
1	10	7	7	23	10	13	0
2	8	9	7	20	6	9	[illegible]
3	7	8	5	20	4	7	3
4	6	6	5	25	7	10	0
6	11	7	7	20	9	10	8
7	11	8	7	19	5	12	6
8	7	10	7	35	5	10	3
9	5	15	10	25	10	10	0
10	12	17	11	22	10	11	4
11	9	11	9	24	8	12	0
13	8	7	8	32	8	15	0
14	13	11	9	25	6	10	3
15	10	11	9	30	10	12	0
16	9	7	6	34	11	9	0
17	10	9	8	25	10	15	0
18	9	17	11	30	10	15	5
19	6	9	5	22	9	10	0
20	7	8	5	21	7	8	0
21	11	7	8	22	13	15	0
22	4	6	4	20	2	7	0
23	10	10	6	31	3	6	0
24	9	7	6	30	9	10	0
25	11	12	7	25	10	11	0
26	13	10	10	20	13	10	0

RA = right atrium RV = right ventricle

wide spectrum like their clinical features and that this should be determined mainly by the function of the tricuspid valve rather than by the condition of the proximal chamber

In the patients of the Tricuspid Stenosis Dominant Type who show severe symptoms the blood flow into the distal chamber in diastole is reduced by the tricuspid stenosis, resulting in the elevation of the right atrial pressure with the right to left shunt and the decrease of the pulmonary flow In this type of patient, the deformity is extreme and particularly as evidenced in cases No 5 and 6 the small distal chamber further reduces the output of the right ventricle

In the patients of the Tricuspid Insufficiency Dominant Type tricuspid insufficiency results in a back and forth flow of a large amount of blood between the right atrium and right ventricle and necessitates the volume overwork of both chambers resulting in severe dilatation The mild symptoms in three patients of this type make it likely that an adequate cardiac output should be maintained despite the severe tricuspid insufficiency The proximal chamber was relatively small compared to the dilated right atrium or the right ventricle, so it was apparent that this portion had little effect on the hemodynamics

Dilatation of the right ventricular outflow tract which was demonstrated as the double ball sign in angiocardiography was most prominent in the patients of the Tricuspid Insufficiency Dominant Type and it might be attributed to severe tricuspid insufficiency However, the double ball sign was also observed in patients of the Tricuspid Stenosis Dominant Type who might have a mild or no tricuspid insufficiency In addition the outflow tract in diastole was enlarged to various degrees in all patients of the Mild Type, but it was not sufficient to show the double ball sign Based on these findings, the enlargement of the outflow tract in this anomaly should be considered to be a part of the inherent defect

In the patients of the Mild Type it can be seen from the clinical data described previously that the function of the tricuspid valve is relatively good and that adequate pulmonary flow is maintained

With a properly functioning tricuspid valve and

Polymicrobial infective endocarditis An increasing clinical entity

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Among the 203 cases of infective endocarditis seen between 19o3 and 1969 at the Henry Ford Hospital only one patient had polymicrobial (mixed infection) endocarditis and this case occurred after cardiac surgery Since that time we saw nine patients with this infection Furthermore over the last two years a polymicrobial etiology was found in 10 per cent of all of our endocarditis patients

This experience contrasts with the 1942 report of Orgain and Poston of six cases of mixed infection in bacterial endocarditis and their observation that endocarditis due to more than one organism was very uncommon Furthermore Weinstein and Rubin found only one case of polymicrobial endocarditis in a review of 452 cases of infective endocarditis occurring from 1951 to 1966 Since then at least 21 other cases were reported by various authors with as many as four pathogens isolated in one patient

The purpose of this paper is to describe the clinical features bacteriology and therapy of our cases review reported cases and compare endocarditis due to single and multiple organisms

Patients and methods

Patients Patients with polymicrobial endocarditis were retrospectively studied The nine cases seen since 1969 were in heroin addicts one of whom had recent aortic valve surgery (patient No 1 Tables I and II) while the first case encountered in 19o8 occurred in a *non addict* after cardiac surgery (patient No 10) The criteria for the diagnosis included (1) polymicrobial bacteremia with the same organisms isolated in each of six or more blood cultures obtained over 24 hours or the isolation of two or more organisms from heart valve cultures at the time of surgery or postmortem examination (2) significant cardiac murmurs (3) fever and (4) embolization These criteria were modified after Menda and Gorbach [8]

Treatment regimens Antibiotic therapy was started empirically during the first two days of admission in all ten patients as clinical evidence for a diagnosis of endocarditis was present In all cases when blood culture results were available definitive antibiotic therapy was selected on the basis of in vitro studies All patients received six weeks or more of antibiotic treatment except two who died at 4 and 19 days respectively

Antimicrobial activity The MIC (minimal inhibitory concentration) and MBC (minimal bactericidal concentration) of the antibiotic used for treatment of patients with bacterial endocar

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Mild Type ocupy 54 per cent of the total In cases such as this, it is difficult to decide on the suitability of operation Genton and Blount[7] reported that the patients over 50 years of age had generally enjoyed good health, that cyanosis was present in only about 50 per cent, and that the cardiac silhouette on the x ray film was often nondescript but appeared to be normal or nearly so in some cases[7] One of the two patients who lived till 79 years of age was asymptomatic and the other had no cardiomegaly[2, 9] These patients would be included in the Mild Type of this report Their prognosis seems to be good, and especially some patients without any cyanosis nor symptoms may be able to live out their natural lives However careful observation must be made of the patients with mild cyanosis because they may deteriorate at some stage in their life

Summary

Twenty six patients with Ebstein's anomaly were classified into three types according to their clinical features, heart catheterization data, angiocardiographic and anatomical findings which were obtained on surgery or autopsy The hemodynamics in each type were discussed

1 Tricuspid Stenosis Dominant Type Eight patients who were cyanotic and had severe symptoms mild to moderate cardiomegaly, and the double ball sign on angiocardiography were classified into this type A pressure gradient across the tricuspid valve was demonstrated in 5 patients

Tricuspid stenosis restricts the blood flow into the functioning right ventricle and results in the low output of the right ventricle and right to left shunt at the atrial level

2 Tricuspid Insufficiency Dominant Type Four cyanotic patients who had mild symptoms despite the severe cardiomegaly were grouped into this type The double ball sign was found in all In three patients incompetent tricuspid valve was observed

Tricuspid insufficiency necessitates the volume overwork of the right atrium and the functioning right ventricle, resulting in severe dilatation

3 Mild Type Fourteen patients who showed no or mild cyanosis, no or mild symptoms and mild to moderate cardiomegaly, were classified into this type

It is considered that the adequate cardiac output in these patients is attributable to the good function of the tricuspid valve

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heroin associated cases while the heroin unrelated surgical patient developed fever nine weeks postoperatively

All were febrile on admission (38 6 to 40 C) Shaking chills were noted by eight and pleuritic chest pain occurred in six Septic pulmonary emboli were confirmed in two patients by multiple pulmonary infiltrates on chest x ray or lung scans that demonstrated multiple perfusion defects

Seven of the ten had murmurs on admission and the remaining three developed a murmur within the first 24 hours after admission In all ten the valve involved was later demonstrated by echocardiography cardiac catheterization or postmortem examination Echocardiograms were positive in five and cardiac catheterization was performed in six of the ten

Splenomegaly was found in two patients and splenic infarction confirmed in another at autopsy Two patients had multiple Roth spots while another patient had both Roth spots and *Candida chorioretinitis* on ophthamologic examination Another (patient No 6) developed a septic arthritis of the left sacroiliac joint early in the course of treatment

Two patients died One (patient No 8) presented in coma with hemiparesis secondary to a ruptured mycotic aneurysm of the internal carotid artery This patient also had a brain abscess and purulent meningitis Another (patient No 9) developed congestive failure on the second hospital day due to acute aortic insufficiency and died

The tricuspid and mitral valves were most commonly affected Three patients had tricuspid insufficiency two had mitral insufficiency two had aortic insufficiency and one had both tricuspid and mitral insufficiency The heroin related postsurgical patient with an aortic prosthesis developed endocarditis involving both the aortic and mitral valves The non heroin related postsurgical patient had an atrial septal defect repair and also developed endocarditis of the mitral valve

Laboratory studies Nine patients all heroin addicts had leukocytosis on admission ranging from 10 800 to 48 000/mm Anemia was present in all patients At admission the mean hemoglobin was 11 5 Gm /100 ml (range 10 0 to 13 8 Gm / 100 ml)

The most common organism encountered was

Table II Summary of causative organisms serum bactericidal activity and antimicrobial therapy

Case no	*Organism*	*Peak SBT**	*Antibiotic therapy*
1	S viridans	1 128	Ampicillin plus
	H influenza	1 4096	Gentamicin
	H parainfluenza	1 256	
	S epidermidis	1 256	
2	S aureus	1 64	Cephalothin
	Beta streptococcus (group B)	1 128	
3	Corynebacterium	1 2	Vancomycin plus
	C parapsilosis	1 2	Amphotericin plus Flucytosine
4	S aureus	1 128	Methicillin plus
	P aeruginosa	1 8	Tobramycin plus Carbenicillin
5	Beta streptococcus (non group A)	1 512	Penicillin G plus
		1 512	Gentamicin
	Streptococcus (non group D)		
6	P aeruginosa	1 16	Carbenicillin plus
	S faecalis	1 128	Tobramycin plus Ampicillin
7	S aureus	1 512	Cefazolin plus
	P aeruginosa	1 16	Carbenicillin plus Gentamicin
8	S faecalis	1 8	Ampicillin plus
	P aeruginosa	N D †	Streptomycin
9	S faecalis	N D †	Methicillin
	P aeruginosa		
10	S epidermidis	N D †	Penicillin plus
	S viridans	N D †	Streptomycin

*Serum bactericidal titer against specific organisms isolated
†Not done

P aeruginosa in five patients followed by *S faecalis* and *S aureus* in three *Candida parapsilosis* corynebacteria *H influenza* *H parainfluenza* *S epidermidus* and four different strains of *streptococci* were the other organisms isolated The most common combinations of organisms were *S faecalis* and *P aeruginosa* in three cases and *S aureus* and *P aeruginosa* in two

Treatment and outcome Multiple antibiotics were usually employed (8 of 10 cases) as illustrated in Table II On the other hand antibiotic therapy with cephalothin alone was given in one case (patient No 2) since both organisms were susceptible to this antibiotic In the only other case (patient No 9) treated with a single antibiotic the second organism was not isolated from the initial culture until after the patient had died

Of the eight patients given antibiotic therapy

Table I Clinical features of ten patients with polymicrobial endocarditis treated at the Henry Ford Hospital

Case no	*Age & sex*	*Race*	*Addiction*	*Post surgery*	*Valve*	*Organism*	*Surgical treatment*	*Outcome*
1	25 M	B	+	+	Aortic Mitral	S viridans H influenza H parainfluenza S epidermidus	None	Cured
2	24 F	B	+	–	Mitral	S aureus B streptococcus (group B)	None	Cured
3	39 M	B	+	–	Aortic	Corynebacterium C parapsilosis	Aortic valve replacement	Cured
4	25 M	B	+	–	Tricuspid	S aureus P aeruginosa	None	Relapsed with P aeruginosa Subsequently cured with gentamicin carbenicillin and probenicid
5	24 M	B	+	–	Tricuspid	B streptococcus (non group A) Non hemolytic streptococcus (non group D)	None	Cured
6	24 M	B	+	–	Mitral Tricuspid	P aeruginosa S faecalis	None	Cured
7	26 M	B	+	–	Tricuspid	S aureus P aeruginosa P aeruginosa	Tricuspid valvulectomy	Cured
8	37 M	B	+	–	Mitral	S faecalis P aeruginosa	None	Died on 19th hospital day
9	25 M	B	+	–	Aortic	S faecalis P aeruginosa	Scheduled for aortic valve replacement	Died on 4th hospital day
10	30 M	W	–	+	ASD Mitral	S albus S viridans	None	Relapsed ×2 with S epidermidus alone Subsequently cured with Penicillin and Streptomycin

ditis were determined by the twofold dilution technique using trypticase soy broth (BBL) The inoculum consisted of approximately 10' organisms The MIC was defined as the lowest concentration of antibiotic that inhibited visible growth of bacteria after incubation for 18 hours at 37° C The MBC of each isolate was defined as the highest dilution from which no more than 20 colonies grew after 0 01 ml loopful was subcultured on 10 per cent sheep blood agar and incubated overnight When vancomycin was used the end point was 50 rather than 20 persisting colonies

Bactericidal titers of serum were determined by the twofold dilution technique with trypticase soy broth as the diluent using a similar inoculum and end point as described above

Results

Clinical features The salient features of our ten patients are summarized in Table I The age ranged between 24 and 39 years with a mean age of 27 9 years There were nine males and one female The female patient was diagnosed and treated during the second trimester of pregnancy Nine were heroin addicts some for as long as 11 years While eight had no previous history of cardiac disease two had previous cardiac surgery One patient had undergone a repair of an atrial septal defect nine weeks earlier and one of the heroin related cases had an aortic valve replacement three months prior to developing polymicrobial endocarditis The average duration of symptoms was 16 days prior to seeking medical attention with a range of 3 to 35 days in the

instances clinical features were present that suggested a second organism One (patient No 6) addict while being treated for enterococcal endocarditis developed septic arthritis of the sacroiliac joint Monoarticular septic arthritis and adjacent flat bone osteomyelitis have been described in heroin addicts and are usually due to *S aureus* and *P aeruginosa* [1] The latter organism was subsequently recovered from initial blood cultures With less virulent organisms such as viridans streptococci or enterococci migratory polyarthritis has been described but septic arthritis is rare [1]

In another patient (patient No 3) the presence of *Candida chorioretinitis* and Roth spots suggested a polymicrobial etiology Roth spots may be associated with either bacterial or fungal endocarditis but chorioretinitis or endopthalmitis is suggestive of a fungal etiology [2] In this patient blood cultures revealed corynebacterium after 48 hours of incubation while *C parapsilosis* was identified after 5 days

In the last instance (patient No 6) when blood cultures initially grew only *S faecalis* septic pulmonary emboli suggested an additional etiologic agent Septic pulmonary emboli occur in endocarditis due to more virulent organisms infecting the tricuspid valve With organisms such as viridans streptococci or enterococci emboli do not occur possibly because these organisms do not usually infect right sided valves [1] In this patient after 96 hours of incubation the initial blood cultures also grew *P aeruginosa*

Antimicrobial therapy we employed usually was with a combination of agents appropriate for each organism Although increased adverse reactions may have been expected they were not encountered possibly because we did not routinely utilize high dose (> 5 mg /Kg /day) aminoglycoside therapy in the treatment of gram negative bacillary endocarditis

In our series as well as in previous reports of endocarditis due to a single agent gram positive organisms were eradicated when peak bactericidal titers 8 to 32 times the minimal inhibitory concentrations were achieved

As reported by others eradication of gram negative bacilli causing endocarditis did not relate to peak serum bactericidal titers This in part may relate to falsely elevated in vitro titers which can result from alkalinization of serum which occurs on standing Recent reports showed that the use of aminoglycoside antibiotics at dosages generally considered toxic were associated with a higher percentage of medical cures in endocarditis due to gram negative bacilli [2] One in our series (patient No 4) who relapsed was cured when retreated with carbenicillin probenecid and an aminoglycoside at doses of 150 per cent those originally utilized

Surgery plays a significant role in the treatment of patients with polymicrobial endocarditis While 15 per cent of patients with single organism endocarditis may need surgery 52 per cent of patients with polymicrobial endocarditis required surgery The high incidence of surgery may relate to the frequent occurrence of Candida (23 per cent) and *P aeruginosa* (29 per cent) as causative agents Fungal endocarditis is seldom cured medically and surgical extirpation of the infected valve may be required [5, 2] In Pseudomonas endocarditis medical failure has been common and surgical removal of the valves has been used for intractable infection [22] Finally *S aureus* present in more than 50 per cent of the endocarditis patients in this series is frequently associated with residual valvular disorders such as aortic insufficiency which may require surgery for intractable failure

This study and recent reports therefore indicate that polymicrobial endocarditis occurs mainly in patients abusing heroin and/or having recently undergone cardiac surgery To decrease mortality rate and morbidity early aggressive antibiotic therapy may be indicated even in a suspected case of polymicrobial endocarditis Specific therapy should be selected on the basis of in vitro studies for each causative organism The ultimate outcome of a patient with polymicrobial endocarditis was related to the type of infecting pathogen rather than to the number of pathogens present Treatment usually required use of two or more antibiotics and adverse effects may be encountered since toxic doses of aminoglycosides may be necessary to eradicate gram negative bacilli When a fungus is one of the organisms cultured or if hemodynamically significant abnormalities occur early surgery should be considered as patients with polymicrobial endocarditis are usually young and otherwise healthy

Summary

Polymicrobial endocarditis was very uncommon until ten years ago However since that time at least 21 cases were reported and 10 patients with this mixed infection were seen at

Table III Summary of treatment and outcome of 31 cases of polymicrobial endocarditis

Reference	No of cases	Treatment		Heroin related	Postcardiotomy	Died
		Medical	Medical & surgical			
(1969 71) Reyes et al[4]	1	1	3	4	0	1
(1971 72) Harris et al[5]	4	0	4	4	0	1
(1967 71) Banks et al	3	1	2	3	0	2
(1971) Menda & Gorbach	1	1	0	1	0	0
(1969 71) Dreyer & Fields	1	NG	NG	1	0	0
(1967) Childs et al[9]	1	1	0	1	0	0
(1968 69) Hermans & Washington	3	NG*	NG*	0	3	[illegible]
(1971) Simberkoff[1] et al	1	0	1	1	0	0
(1969 74) Mills & Drew[1]	3	2	1	2	0	2
(1958 75) Current series	10	7	3	9	2	2
Total	31	13/27	14/27	26	5	10
Per cent		48	52	84	16	32

Not given

alone, six were cured, although two required a second course of antibiotics The two treatment failures in this group were due to inappropriate antibiotics (patient No 8) and acute aortic insufficiency (patient No 9)

Of the two patients given antibiotic therapy combined with surgical excision of the infected valve (patients No 3 and 7) both were cured One, with Candida endocarditis was aggressively managed after several days of antibiotic therapy based on presently recognized methods of managing such infections The other patient had Pseudomonas tricuspid endocarditis and was treated surgically after relapse following antibiotic therapy

Summary of review of reported cases As previously noted polymicrobial endocarditis was an uncommon occurrence prior to 1966 At least 21 cases of polymicrobial endocarditis were reported since 1966 (Table III) Seventeen of these (81 per cent) were related to heroin use three (14 per cent) occurred after cardiac surgery and one patient had rheumatic heart disease In these cases, the most commonly encountered organisms were *S aureus* (14) Candida (six) non-group D streptococci (five) *P aeruginosa* (four) and Serratia (three)

When the 21 cases previously reported are combined with our ten cases (Table III) only 48 per cent were treated with medical therapy alone In addition 52 per cent needed cardiac surgery either for treatment of intractable infection or repair of hemodynamically significant problems related to the infection Finally, even with aggressive combined medical and surgical therapy, the mortality rate was 32 per cent

Discussion

Recently mixed or polymicrobial bacteremias have become frequent In 1970 Hermans and Washington reported[7] a 6 per cent incidence among all patients with bacteriologically established bacteremia Patients identified as being at high risk for mixed infections were premature infants and patients with hematologic malignancies or gastrointestinal diseases Recognition of polymicrobial bacteremia is important, because it is associated with high mortality rate (37 to 81 per cent)[7, 1] Furthermore these investigators reported only three patients with the rare entity of polymicrobial endocarditis or endarteritis among the 46 cases of polymicrobial bacteremia All three cases followed cardiac surgery Only two of our ten cases had undergone previous cardiac surgery On the other hand the patient profile in the other eight patients with mixed endocarditis was quite different They were young heroin addicts with no prior underlying cardiovascular disease

In our cases polymicrobial endocarditis was usually indistinguishable from endocarditis caused by a single organism However in three

Abrupt propranolol withdrawal in angina pectoris Effects on platelet aggregation and exercise tolerance*

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Propranolol has been shown conclusively to be a relatively safe and efficacious drug for the treatment of most patients with angina pectoris In dosage sufficient to improve exercise tolerance it has also been demonstrated to restore towards normal the increased platelet aggregability noted in patients with angina pectoris However it has recently been suggested that abrupt discontinuation of propranolol after long term therapy may have adverse effects precipitating myocardial infarction and sudden death To further evaluate the possible mechanisms for the occasional adverse clinical effects of propranolol withdrawal data are presented from a study designed to measure exercise tolerance and platelet aggregation in patients with angina pectoris before during and after propranolol treatment The protocol for study was devised and carried out before reports appeared suggesting possible adverse effects from abrupt withdrawal of the drug Because of these reports the accumulated data were analyzed for possible rebound effects and the results form the subject of the present study

Methods

Patients The study population consisted of 20 patients 14 men and 6 women aged 35 to 69 (mean 54) years of age Criteria for inclusion were (1) at least three attacks of angina pectoris per week with no evidence of an accelerated course (unstable angina) in the 6 months prior to study (2) absence of valvular heart disease hypertension congestive heart failure chronic obstructive pulmonary disease diabetes lipoprotein abnormalities anemia smoking history or myocardial infarction within 6 months of study, and (3) angiographic narrowing of at least 70 per cent of one or more of the coronary arteries and definite electrocardiographic (ECG) evidence of myocardial ischemia associated with chest pain during submaximal exercise stress testing

Ten age and sex matched normal subjects with a negative exercise stress test were also studied These normal subjects had no evidence of ischemic vascular disease lipid abnormalities or diabetes and each had a negative history for cigarette smoking and drug ingestion of any sort

Experimental design All normal subjects had platelet aggregation studies and exercise tests as described below

The patients with angina pectoris were seen biweekly by the same physician Informed consent was obtained and all cardiovascular medications were discontinued with the exception

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our hospital All, except one of these infections, occurred in patients who had undergone heart surgery or abused intravenous drugs Although generally clinically indistinguishable from mono microbial endocarditis, these mixed infections carried a very high mortality rate (> 30 per cent) and an unusually large number of the patients (> 50 per cent) needed heart surgery either to control the infection or to repair cardiac defects resulting from the infection The prognosis depended on the species rather than the number of organisms isolated and on aggressive antimi crobial and surgical therapy

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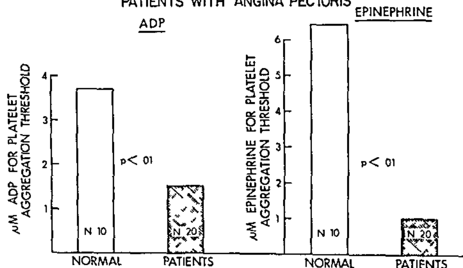


Fig 2 Comparison of ADP and epinephrine induced platelet aggregability in normal subjects and patients with angina pectoris Platelets of normal subjects require significantly higher concentrations of ADP *(left panel)* and epinephrine *(right panel)* to attain aggregation threshold than do platelets of patients with angina pectoris

analysis The specimens were coded so that those performing the aggregation studies had no knowledge of the patient the diagnosis or type of drug therapy

Platelet aggregation studies were performed using the turbidometric method of Born as modified by Mustard and colleagues [3] and previously reported from this laboratory [3] The aggregating agents used were ADP and epinephrine The ADP concentrations producing irreversible aggregation in untreated patients and normal subjects were 0 5 1 2 5 10 20 and 100 μM comparable epinephrine concentrations for aggregation were in the range of 0 05 to 5500 μM The lowest concentration producing a full biphasic response was recorded as the threshold dose the threshold concentration of ADP and epinephrine was assessed without extrapolation between different concentrations The change in light transmittance to increasing concentrations of ADP and the characteristic biphasic response at the threshold are illustrated in Fig 1 In repeated ADP and epinephrine determinations using coded samples reproducibility was within 10 per cent of mean

Exercise testing Bicycle ergometry testing was performed by another examiner who had no knowledge of the subject s drug status during the study A modification of the ear ensiform system of Arbarquez and associates [14] was used with three apical leads recorded in the supine position and on the bicycle ergometer prior to exercise

Multistage graded exercise was performed utilizing a bicycle ergometer (Schwinn ergometric exerciser) as the patient pedaled against a predetermined load After blood for platelet studies had been obtained patients were started at a work load of 150 k p m /minute which was increased in increments of 150 k p m every three minutes until chest pain fatigue or a heart rate of 150 per minute occurred An abnormal electrocardiographic response was defined as a flat or down sloping ST segment depression of at least 1 mm persisting for at least 0 08 sec after the termination of the QRS complex with the P Ta segment as the baseline of reference

Blood pressure in the brachial artery was recorded by sphygmomanometer prior to and immediately after exercise The heart rate blood pressure product an indirect assessment of myocardial oxygen consumption [5] was calculated from measurements obtained immediately after cessation of exercise

The incidence of other ECG changes (bundle branch block patterns ventricular premature contractions) was also noted

Propranolol blood levels Assay of the level of propranolol in blood was performed on coded

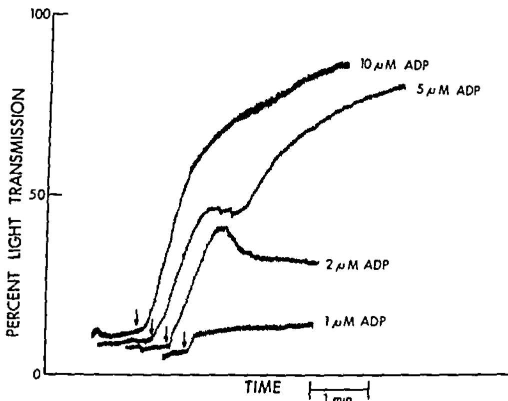


Fig 1 Aggregation response of platelets from a normal subject induced by increasing concentrations of adenosine diphosphate *(ADP)* Degree of aggregation is related to the increase in light transmission since clumping reduces light absorption ADP is added to stirred platelet rich plasma *at the arrows* 5 μM ADP induces the characteristic biphasic aggregation threshold response of an initial plateau followed by maximal aggregation 1 μM and 2 μM ADP are inadequate to achieve threshold of maximal aggregation 10 μM ADP induces maximal aggregation but at this higher concentration the biphasic threshold cannot be detected (From Frishman W Weksler B Christodoulou J et al Reversal of abnormal platelet aggregability and change in exercise tolerance in patients with angina pectoris following oral propranolol Circulation 50 887 1974 Reproduced by permission of the American Heart Association Inc)

of nitroglycerin An oral placebo* was administered for 6 weeks Every patient had a resting electrocardiogram chest roentgenogram urinalysis and blood analysis for cholesterol triglycerides glucose blood urea nitrogen creatine phosphokinase (CPK) lactic dehydrogenase (LDH) serum glutamic oxaloacetic transaminase (SGOT) hematocrit hemoglobin white blood cell count and platelet count Platelet aggregation studies were performed and exercise testing on a bicycle ergometer was carried out as described below After the 6 week placebo period subjects with angina pectoris were randomized into placebo (n = 10) and propranolol (n = 10) treatment groups The placebo group remained on the same placebo regimen while the drug treatment group was started on 160 mg daily of oral propranolol in 4 divided doses Neither the patient nor the physician knew whether the therapy was placebo or drug All patients continued taking nitroglycerin as needed After 16 and again after 50 weeks of therapy serum propranolol levels were determined and platelet aggregation studies and exercise tolerance tests were repeated At this time both placebo and propranolol therapy was abruptly stopped In the propranolol treated group five patients were withdrawn and given placebo and five received no further medications whatsoever Final propranolol blood levels, platelet aggregation studies and exercise tolerance tests were repeated 48 hours after cessation of the study medications

Platelet aggregation studies Blood was obtained after a twelve hour fast Following an initial resting period of 30 minutes a 19 gauge needle was inserted without use of a tourniquet into an antecubital vein and a slow infusion of physiological saline begun After 15 minutes of rest with the patient relaxed blood was sampled by free flow into plastic tubes containing 1/10 volume acid citrate dextrose (ACD) The blood specimens were then immediately processed for

*Mannitol ??, mg (Ayerst Laboratories)

Table IB Individual and group mean (geometric mean) concentrations of ADP and epinephrine induced platelet aggregation in patients with angina pectoris treated with propranolol and placebo and following abrupt treatment withdrawal*

Angina placebo treated	*Age*	*Control*		*Placebo (16 weeks)*		*Placebo (50 weeks)*		*Withdrawal*	
		ADP (μM)	*Epi (μM)*	*ADP (μM)*	*Epi (μM)*	*ADP (μM)*	*Epi (μM)*	*ADP (μM)*	*Epi (μM)*
1	54	2	5 [illegible]	?	5 5	1	5 5	1	[illegible] 5
2	60	?	5 5	?	0 5	2	0 5	2	0 5
3	48	?	0 5	2	0 5	5	5 5	2	5 5
4	38	5	0 5	?	5 5	2	0 5	5	0 5
5	54	?	5 5	5	0 5	1	5 5	1	27 5
6	55	2	5 5	1	5 5	2	0 5	0 5	5 5
7	40	2	0 5	2	5 5	2	0 5	2	0 5
8	59	2	0 5	2	5 5	1	0 5	2	0 5
9	57	1	5 5	1	0 [illegible]	2	[illegible] 5	1	5 5
10	53	0 5	0 5	1	0 5	0 5	[illegible] 5	2	0 5
		1 8	1 4	1 78	1 4	1 55	1 4	1 55	1 32

Angina–propranolol treated	*Age*	*Control*		*Propranolol 160 mg per day (16 weeks)*		*Propranolol 160 mg per day (50 weeks)*		*Withdrawal*	
		ADP (μM)	*Epi (μM)*	*ADP (μM)*	*Epi (μM)*	*ADP (μM)*	*Epi (μM)*	*ADP (μM)*	*Epi (μM)*
1	5	5	0 5	5	5 5	5	27 5	5	0 5
?	60	[illegible]	0 5	5	5 5	5	5.5	5	0 0[illegible]
3	34	2	0 5	2	[illegible] 5	5	5 5	1	0 0[illegible]
4	48	2	[illegible] 5	5	5[illegible] 0	2	55 0	1	0 5
[illegible]	54	2	0 [illegible]	2	[illegible] 5	5	27 5	2	0 [illegible]
6	57	2	5 5	[illegible]	55 0	5	27 5	2	0 5
7	48	?	0 5	[illegible]	27 5	10	2[illegible] 5	2	0 [illegible]
8	50	?	5 5	5	27 5	5	55 0	1	5 5
9	[illegible]9	1	0.5	5	5 5	5	5 5	1	0 5
10	[illegible]	1	0 5	2	5 5	5	27 5	.5	0 5
		1 3?	1 0?	3 43†	12 9†	4 9‡	13 2‡	1 0§	0 57§

See T bl 1A for bb n t n and oth rs footnotes

angina pectoris In the 10 patients who received propranolol (160 mg /day) total work increased by 130 per cent from a control of 765 ± 125 k p m to 1 790 ± 285 k p m after propranolol (p < 0 01) This beneficial effect on work performance was associated with a significant drop in the heart rate blood pressure product from 16 800 ± 1540 to 12 000 ± 885 after propranolol (p < 0 01) In 10 patients on propranolol typical anginal pain still was the end point

Forty eight hours after abrupt propranolol withdrawal all patients returned to their pretreatment exercise tolerance level In some instances performance was less than the control state After 50 weeks of propranolol therapy just prior to drug withdrawal mean work level was 1 690 ± 200 k p m but fell 63 per cent to 630 ± 1?0 k p m (p < 01) 48 hours after propranolol cessation (Fig 7 Table II) The product of heart rate and blood pressure (RH × BP was 11 200 ± 1 300 after 50 weeks of propranolol therapy and increased to 15 500 ± 513 following drug withdrawal (p < 01) (Fig 8 Table II) The decline in work performance was similar whether propranolol treated patients were withdrawn *onto placebo* or off all treatment There were no significant differences in work performance or *HR × BP* in placebo treated patients when values obtained during the control period during placebo therapy and after withdrawal of placebo were compared

All patients withdrawn from propranolol noted increased frequency of anginal pains however no myocardial infarctions or arrhythmias occurred Propranolol therapy was quickly reinstituted in all patients following completion of studies No

Table IA Individual and group mean* concentrations of ADP and epinephrine induced platelet aggregation in normal subjects

Normal subjects	*Age*	*ADP (μM*)*	*Epi (μM*)*
1	47	2	5 5
2	46	5	5 5
3	55	5	5 5
4	45	2	27 5
5	56	5	27 5
6	54	5	27 5
7	52	10	5 5
8	48	5	0 5
9	60	1	5 5
10	55	5	5 5
		3 72	6 46

Abbreviations ADP adenosine diphosphate Epi = epinephrine
Geometric mean
†Values different from control value at $p < 0 01$ confidence level
‡No significant difference compared to values at 16 weeks.
§Values different from 50 weeks at $p < 0 01$ confidence level no difference compared to control value.

samples obtained at least 2 hours after the last tablet of propranolol or placebo was ingested and just prior to exercise testing The serum levels were measured in double blind fashion, using the fluorometric methods of Black and colleagues[16] as modified by Coltart and Shand [17]

Statistical analysis For all of the variables except platelet aggregation data arithmetic means with the standard error of the mean are presented and Student s t test for paired and unpaired data were employed For aggregation data geometric means are presented Geometric means are preferred since the concentrations of ADP and epinephrine used were essentially geometric dilutions The Wilcoxon Rank Sum Test was used for tests of significance comparing platelet aggregability of normal subjects untreated angina patients and treated angina patients Comparison of aggregation data from the same patient group treated with various experimental protocols were done with the Wilcoxon Signed Rank Test and the Sign Test

Results

Platelet aggregation studies Before propranolol therapy, patients with angina pectoris demonstrated increased platelet sensitivity to aggregating concentrations of both ADP and epinephrine when compared with normal subjects The mean concentration of ADP necessary for the biphasic threshold response and maximal aggregation was 1 55 μM in patients and 3 72 μM in normal subjects, ($p < 01$) Mean epinephrine concentration for maximal aggregation was 1.26 μM in patients and 6 46 μM in normal subjects ($p < 01$) (Fig 2 Table I)

Serial studies performed on the patients receiving placebo showed no change in the increased platelet sensitivity to either ADP or epinephrine Following abrupt placebo withdrawal, no change in platelet aggregation threshold was observed (Figs 3 and 4, Table I)

Administration of propranolol in a dose of 160 mg per day had a dramatic effect in reducing platelet sensitivity to ADP and epinephrine in patients with angina pectoris After 16 weeks of propranolol therapy a mean of 3 43 μM ADP was required to produce a biphasic aggregation response compared to 1 32 μM before therapy ($p < 01$) With epinephrine, 12 9 μM was required after propranolol therapy in contrast to 1 02 μM before therapy ($p < 01$) No additional changes were noted in ADP or epinephrine platelet aggregation threshold after 50 weeks of propranolol therapy

Following abrupt propranolol withdrawal, harvested platelets demonstrated marked increase in sensitivity to aggregating agents Only 1 0 μM ADP was now required to aggregate platelets and only 0 57 μM epinephrine threshold values significantly lower than the aggregating concentrations required during propranolol therapy (Figs 5 and 6 Table I) In six of 10 patients the platelets were even more hyperaggregable than in the control state before initiation of propranolol therapy

Mean serum concentration of propranolol was 47 ± 9 ng /ml (range 25 to 120 ng /ml) at a dose level of 160 mg per day and 1 ± 8 ng /ml 48 hours after treatment withdrawal

There were no significant changes from control in the mean levels of blood glucose urea nitrogen serum glutamic oxaloacetic transaminase creatine phosphokinase lactic dehydrogenase cholesterol triglycerides hematocrit or platelet count during the serial sampling periods or after abrupt propranolol withdrawal

Exercise tests During the control period all 20 patients with angina pectoris had a positive electrocardiographic response to exercise Administration of propranolol was followed by significant increase in exercise tolerance in the patients with

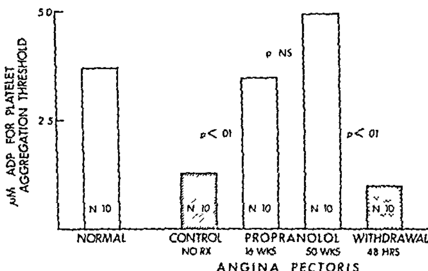


Fig 5 Effect of propranolol and its sudden withdrawal on ADP induced platel t aggregability in patients with angina pectoris After propranolol, platelets of treated patients are less sensitive to ADP (geometric mean) compared to before treatment and not significantly different from normal Forty-eight hours following abrupt propranolol withdrawal platelets of patients have returned to their pretreatment hyper responsiveness to ADP

the heart rate blood pressure product (HR × BP) at the end point of exercise Forty eight hours following propranolol withdrawal exercise tolerance was significantly reduced and HR × BP increased Similar effects occurred whether the patients were withdrawn to placebo or to no treatment As has been shown by others [3] the changes in HR × BP presumably paralleled changes in myocardial oxygen demand Forty eight hours was chosen as the point of restudy following propranolol withdrawal since pharmacological studies have shown that most known cardiovascular effects of the drug are no longer present by that time [4]

This study was performed before the appearance of several case reports citing episodes of myocardial infarction and sudden death following abrupt propranolol withdrawal [1] Subsequently other investigators have noted the same phenomenon in larger series with problems generally occurring within two weeks of propranolol cessation

In this study no cases of myocardial infarction or threatening arrhythmias were observed in patients withdrawn from propranolol but every patient did note a subjective increase in anginal symptoms In each subject therapy was quickly reinstituted following the two day withdrawal study In contrast to the findings seen with propranolol withdrawal no deterioration in exercise performance was noted following withdrawal of chronic placebo therapy nor was there significant change in subjective anginal symptomatology

With the recent recognition that problems may occur following abrupt propranolol withdrawal we reexamined hematologic data obtained in the course of our original study on the hemodynamic and clinical actions of the drug [3]

The mechanism for the propranolol withdrawal effect is unknown and may be related to the multifactorial actions of the drug [15] A likely explanation for the deterioration in exercise performance following drug withdrawal is the loss of sympathetic blockade of cardiovascular function resulting in an acute increase in myocardial oxygen demands in patients with angina pectoris [3] Indeed 48 hours following propranolol cessation there was trace to no detectable drug in the blood Others have documented lack of demonstrable sympathetic blockade at that time [16] Increased angina may be related to greater

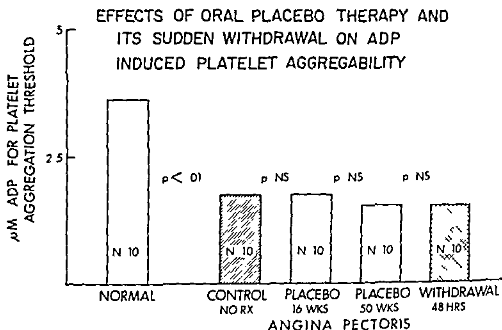


Fig 3 Effects of placebo and its sudden withdrawal on ADP induced platelet aggregability in patients with angina pectoris No changes in platelet sensitivity to ADP are seen during placebo therapy or after its abrupt withdrawal

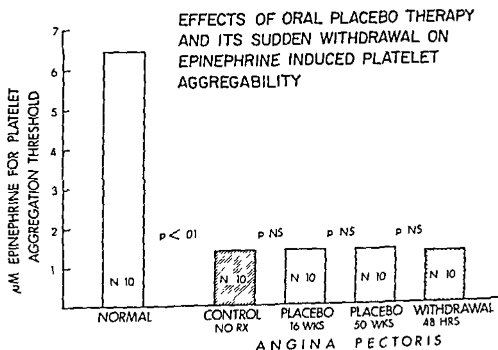


Fig 4 Effects of placebo and its sudden withdrawal on epinephrine induced platelet aggregability in patients with angina pectoris No changes in platelet sensitivity to epinephrine are seen during placebo therapy or after its abrupt withdrawal

changes in frequency of angina were observed in placebo treated patients after withdrawal from placebo

Discussion

Propranolol is an effective agent for treating patients with angina pectoris presumably because it reduces myocardial oxygen requirements during exercise[1,2] It allows the patient to do work while requiring less myocardial oxygen delivery thus delaying the onset of ischemia and the occurrence of chest pain[1]

In this present study, a dramatic improvement in exercise performance was demonstrated during propranolol therapy in patients with angina pectoris associated with a significant decrease in

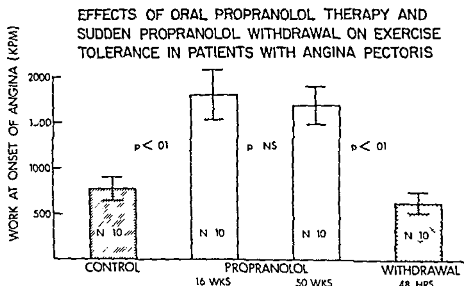


Fig 7 Effects of propranolol therapy and its sudden withdrawal on work performance in patients with angina pectoris A significant mean increase in work performance occurs with propranolol therapy Following abrupt cessation of propranolol mean work performance returned to pretreatment levels Work is measured in kilopond meters (k.p.m)

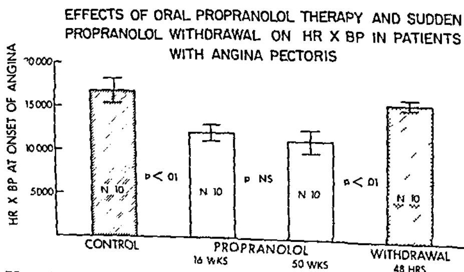


Fig 8 Effects of propranolol therapy and its sudden withdrawal on the heart rate-blood pressure product *(HR × BP)* in patients with angina pectoris. A significant decrease in the *HR × BP* at the onset of angina even though exercise level was higher after treatment is demonstrated after propranolol therapy Following abrupt propranolol withdrawal the HR × BP increases to pretreatment levels

Patients with angina pectoris demonstrated a significant hyperresponsiveness to aggregating concentrations of ADP and epinephrine Propranolol significantly alters ADP and epinephrine induced platelet hyperaggregability towards normal an effect which persists throughout the 50 week treatment period Forty eight hours following propranolol withdrawal at a time when only trace amounts of the drug were present in the serum all patients had returned to their pretreatment hyperaggregable threshold levels In six of 10 subjects platelets were more hyper responsive to aggregating concentrations of ADP and epinephrine than before any treatment However there was no association between the degree of rebound platelet hyper responsiveness and the

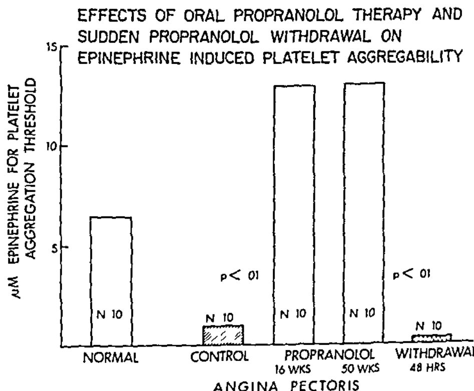


Fig 6 Effect of propranolol and its sudden withdrawal on epinephrine induced platelet aggregability in patients with angina pectoris After propranolol platelets of treated patients are less sensitive to epinephrine (geometric mean) compared to before treatment and not significantly different from normal Forty eight hours following abrupt propranolol withdrawal platelets of patients have returned to their pretreatment hyper responsiveness to epinephrine

oxygen demands of the myocardium released from sympathetic blockade, but whether acute myocardial infarction is related to changes in sympathetic tone is unknown

Decreased affinity of hemoglobin for oxygen and thus improved tissue availability of oxygen has been reported with propranolol therapy [0] Abrupt withdrawal of treatment may possibly result in adverse alterations in oxygen affinity for hemoglobin This finding however, has not been the case in our laboratory and we could not document changes in oxyhemoglobin dissociation in a small group of patients studied in our labora tory under other protocols [19]

Another possible explanation for the occasion ally serious manifestations of propranolol with drawal may be related to the effects of the drug on platelet aggregation [1] Propranolol in dosage sufficient to improve exercise tolerance has been demonstrated to restore towards normal the increased platelet aggregation noted in patients with angina pectoris [3] Further work done in our laboratory has shown a specific platelet mem brane effect of propranolol completely unrelated to its beta blocking properties [21] Platelet aggrega tion was inhibited using concentrations of the drug that could be safely obtained in man

If hyperaggregable platelets play a role in the pathogenesis of ischemic cardiovascular disease as has been suggested by many investigators, an agent which reverses this abnormality may be an important adjunct in chronic treatment At the same time abrupt discontinuation of the agent might trigger detrimental alteration of platelet function contributing to compromised coronary flow by obstruction of the microcircula tion or accumulation of platelet aggregates on atheroma

Myocardial infarction has been observed exper imentally secondary to platelet aggregation, although the aggregates persisted for only a few minutes Haerem[23] reported that platelet aggre gates in the epicardial arteries of patients who died of cardiac causes were more numerous and extensive than those found in patients without cardiac disease Yamazaki and colleagues [2] Haft and Fani [24] and others have suggested experimen tally that hyperaggregable platelets may be playing an important role is ischemic cardiovas cular events

treatment Prior to propranolol mean total work performance was 765 ± 125 k p m HR × BP (heart rate blood pressure product) was 16 800 ± 1 535 Mean platelet aggregation threshold with ADP was 1 32 μM* with epinephrine 1 26 μM* Patients treated with propranolol demonstrated significant improvement in exercise performance (1 790 ± 285 k p m $p < 01$) reduction in HR × BP (12 000 ± 895 $p < 01$) and an elevation in platelet aggregation threshold with ADP 3 43 μM* ($p < 01$) with epinephrine 12 9 μM* ($p < 01$) Following abrupt cessation of propranolol exercise tolerance and HR × BP fell below pretreatment levels (630 ± 117 k p m and 15 500 ± 513 respectively) Similarly platelet aggregation threshold fell to 1 0 μM with ADP and 0 57 μM* with epinephrine In six patients platelets were significantly more hyperaggregable than prior to therapy Anginal frequency increased in all but no acute infarction was observed Abrupt withdrawal of propranolol may be deleterious in patients sometimes causing rebound platelet hyperaggregability associated with increasing anginal frequency and decreasing exercise tolerance

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Geometric mean

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Table II Effects of placebo and propranolol therapy and abrupt treatment withdrawal in patients with angina pectoris

	Patients age			Propranolol blood levels (ng/ml)	Exercise		Platelet aggregation	
	No	Mean (yr)	Sex		Total work (kilopond meters)	Heart rate blood pressure product	ADP µM	Epi µM
Placebo								
Control	10		6M 4F	0	866 ± 122	16 000 ± 467	1 78	1 40
16 weeks	10	52		0	933 ± 136	16 333 ± 416	1 78	1 40
50 weeks	10			0	883 ± 113	16 344 ± 383	1 55	1 40
Withdrawal	10			0	840 ± 136	15 700 ± 484	1 55	1 37
Propranolol								
Control	10		6M 4F	0	765 ± 125	16 800 ± 1 540	1 32	1 01
16 weeks	10	54		54 8 ± 9 2	1 790 ± 265	12 000 ± 885	3 43	12 90
50 weeks	10			47 6 ± 8 4	1 690 ± 200	11 200 ± 1 300	4 90	13 20
Withdrawal	10			1 ± 8	630 ± 117	15 500 ± 513	1 00	0 57

Geometric mean

extent of deterioration in exercise performance or frequency of angina attacks in specific patients following propranolol withdrawal

The exact mechanism of platelet hyperaggregability after acute propranolol withdrawal is not known One could speculate that platelet hyperaggregability may have been related to increased in vivo catecholamine levels or increased sensitivity of platelets to catecholamines, changes in free fatty acid levels [28] or a change in the platelet membrane morphology following disappearance of the drug from the blood Catecholamines have known effect on platelet function [7, 28] and the anxiety associated with the removal of effective therapy may have influenced the results Catecholamine levels were not measured in this study, so that this possibility cannot be totally excluded However, propranolol treated patients withdrawn to placebo appeared no different from patients withdrawn to no therapy and placebo withdrawn patients did not appear more hyperresponsive

As previously described,[3] repeated measurements of human platelet aggregation induced by ADP and epinephrine can be influenced by many patient variables The technique of blood sampling and processing and the rapidity in which platelet studies are performed is critically important [29] Since many drugs influence platelet function studies [30] this factor must be rigidly controlled In this study, considerable effort was devoted to minimizing those patient variables influencing platelet function testing

Whatever the mechanism for the propranolol withdrawal phenomenon it is clear that beneficial effects of the drug sympathetic blockade, improvement in exercise tolerance and normalization of platelet aggregability have disappeared by 48 hours following cessation of propranolol therapy Furthermore, in some patients there is increased platelet hyperaggregability after drug withdrawal

Further work is needed to determine whether platelet hyperresponsiveness continues beyond 48 hours, and if so, for how long, and whether subjects with increased ischemia or infarction are those with the most prominent or long standing effects on platelet aggregability Finally, studies are needed to determine platelet behavior with gradual withdrawal of propranolol as well as the clinical and rheologic implications of adding other agents such as aspirin to block platelet hyperaggregability in this situation

Summary

Data collected before the initial reports of myocardial infarction following sudden withdrawal of propranolol are presented here to evaluate possible mechanisms for this phenomenon Twenty patients with angina pectoris were randomized into placebo and propranolol (160 mg/day) treated groups and followed for 50 weeks at which time treatment was abruptly discontinued Measurements of exercise tolerance the product of heart rate and blood pressure at exercise end point (HR × BP) and platelet aggregation thresholds in response to ADP and epinephrine were made before during and after

treatment Prior to propranolol mean total work performance was 765 ± 125 k p m HR × BP (heart rate blood pressure product) was 16 800 ± 1 535 Mean platelet aggregation threshold with ADP was 1 32 μM* with epinephrine 1 26 μM* Patients treated with propranolol demonstrated significant improvement in exercise performance (1 790 ± 285 k p m p < 01) reduction in HR × BP (12 000 ± 695 p < 01) and an elevation in platelet aggregation threshold with ADP 3 43 μM* (p < 01) with epinephrine 12 9 μM* (p < 01) Following abrupt cessation of propranolol exercise tolerance and HR × BP fell below pretreatment levels (630 ± 117 k p m and 15 500 ± 513 respectively) Similarly platelet aggregation threshold fell to 1 0 μM* with ADP and 0 57 μM* with epinephrine In six patients platelets were significantly more hyperaggregable than prior to therapy Anginal frequency increased in all but no acute infarction was observed Abrupt withdrawal of propranolol may be deleterious in patients sometimes causing rebound platelet hyperaggregability associated with increasing anginal frequency and decreasing exercise tolerance

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Ceom tne m n

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The variability of arterial pressure

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The decision to treat patients with high blood pressure depends largely on the level of pressure. It is therefore important to obtain data from the patient that is truly representative of his average arterial pressure. A major difficulty in evaluating such data is the great variability in the level of blood pressure in any individual patient. Previous workers have attempted to solve the problem by the measurement of blood pressure under standard conditions, for example at rest and on repeated occasions, so as to obtain a representative pressure.[1] The relationship between the indirectly obtained casual blood pressure and the average 24 hour blood pressure sustained by the circulation over 24 hours, is unknown.

Over the last ten years there have appeared from this laboratory a series of publications describing the development and application of a system for continuously recording direct arterial pressure in unrestricted patients.[3] It has now become possible to analyze data collected over a 24 hour period quantitatively in a great deal more depth than was hitherto possible and this paper describes our experience with the latest development of this technique and its use in evaluating the variability of arterial pressure over a 24 hour period.

Patients and methods

Ten patients are included in this study. After informed consent all had their arterial pressure recorded over a 24 hour period as previously described.[1] The details of the ten patients are listed in Table I and all were asymptomatic and none was receiving drug therapy. All ten patients went about their normal daily activities during the course of the study and they slept at home.

Tape analysis system. This system was developed in conjunction with our Departments by the Engineering Division of AERE, Harwell, Berkshire. The system consists of three separate units: (a) a tape replay unit, (b) a blood pressure histogram plotter, and (c) a multi channel analyzer.

The histogram plotter accepts the output for the tape replay unit (speed set at 25 times the recording speed) and derives data in digital form of systolic, diastolic, and mean pressures and measures pulse interval all on a beat to beat basis. The data are held in four registers which sequentially address the memory of the multichannel analyzer at the end of each beat. When the memory is addressed the contents stored at that address are incremented so that a frequency distribution histogram of each of the four parameters builds up. Each parameter is allocated 128 channels in the store of the multichannel analyzer. Each channel size representing 2.5 mm Hg. When the analysis is complete the elements of the four frequency distribution histograms are discharged via a teletypewriter on to paper

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punch tape and these data are subsequently submitted to standard statistical analysis by computer program For each histogram the mean variance and standard deviation were determined It is important to scrutinize the complete 24 hour recording before feeding it through this system in order to avoid inaccurate information due to technical faults or error in the recording procedure The accuracy of this automatic analysis was checked against the direct measurements of the records by two independent observers These two observers agreed with one another with an accuracy of + or −4 per cent and the within observer error was + or −1 per cent Compared with this manual analysis the automatic system corresponded with an accuracy of + or −6 per cent for arterial pressure and heart rate and + or −3 per cent for the total number of beats analyzed The degree of agreement between observer and machine was much greater during the period of sleep when the error was reduced by approximately 50 per cent

Analysis of individual records Records of the ten individual patients were analyzed beat by beat on an hourly basis throughout the 24 hour period In addition the waking and sleeping periods were each averaged sleep being taken as that period from the time that the subject indicated that he was in bed until the time that he was awake again

Statistical methods To test whether the variability of systolic pressure differed from that of diastolic pressure throughout the day and night the Wilcoxon matched pairs signed ranks test was employed Variability was determined from the standard deviation about the mean for each hour

Results

Frequency distribution of blood pressure over 24 hours The frequency distribution pattern of arterial pressure over 24 hours described a bimodal curve (Fig 1) in all but one patient (Case 10) The bimodality was uninfluenced by the over all average pressure The lower mode was due predominantly to the fall of pressure which occurs during sleep (Fig 2) The length of sleep was the single most important factor in determining the shape of the frequency distribution curve (Fig 3)

The variability of arterial pressure Variability of arterial pressure was determined in ten patients from the standard deviation of pressure about the mean for each hour (example Fig 4) Throughout the 24 hour period systolic pressure variation was significantly greater than that in diastolic pressure in all but Case 3 in whom there was no difference This variability was most acutely affected by physical exertion although in individual instances there was marked change in pressure in response to psychological influences During sleep systolic and diastolic pressures both

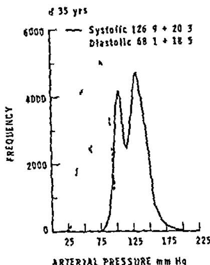


Fig 1 A frequency distribution curve of systolic and diastolic blood pressure in a 35-year old normotensive individual (Case 8) Note the bimodality of both systolic and diastolic pressure and the wide range of pressures covered throughout the 24 hour period

Table 1 Details of 10 patients selected to give a range of different levels of arterial pressure

Case	*Sex*	*Age*	*BSA*	*Casual BP (mm Hg)*	*CXR*	*ECG*	*Biochemical profile*
1	F	53	1 8	200/90	Normal	LV+	Normal
2	M	60	1 8	180/105	Normal	Normal	Normal
3	F	8	1 6	160/110	Normal	LV+	Normal
4	M	76	1 9	130/100	Normal	Normal	Normal
5	F	32	1.5	130/80	Normal	Normal	Normal
6	F	23	1 5	180/110	Normal	Normal	Normal
7	F	44	1 5	160/100	Normal	Normal	Normal
8	M	35	2 0	120/70	Normal	Normal	Normal
9	M	21	1 8	130/90	Normal	Normal	Normal
10	M	20	1 7	165/110	Normal	Normal	Normal

BSA = body surface area CXR = chest radiograph.

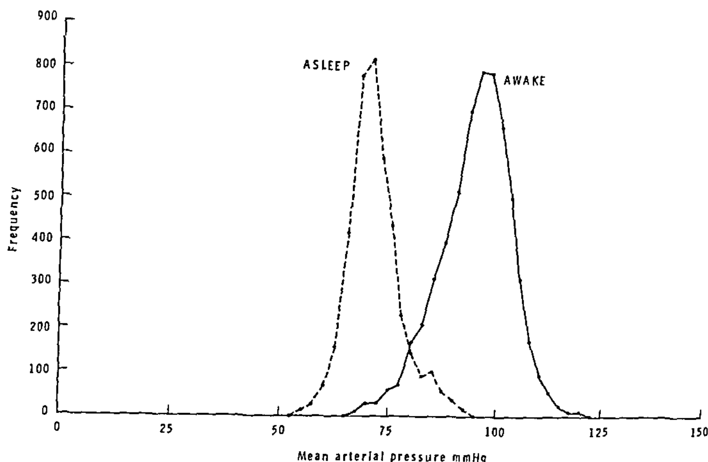


Fig 2 A frequency distribution plot of mean arterial pressure for two separate hours in the day (Case 8) (i) A one hour period during sleep and (ii) a one hour period during waking when the patient was for the majority of the time sitting quietly and not engaged in physical activity Note that during sleep pressure is lower and covers a smaller range than during the waking period

Table II Summary of awake and asleep arterial pressures in the 10 patients whose records were analyzed on an hourly basis

Case	*Awake*						*Asleep*					
	Systolic	*S D*	*Diastolic*	*S D*	*Mean*	*S D*	*Systolic*	*S D*	*Diastolic*	*S D*	*Mean*	*S D*
1	216	26	108	12	145	15	122	13	70	7	92	7
2	140	15	109	12	127	11	110	8	90	7	102	8
3	138	18	91	9	106	9	112	8	79	5	92	6
4	144	29	63	22	94	20	105	14	49	16	75	15
5	182	26	115	15	141	16	132	11	81	7	103	8
6	131	13	124	11	132	11	109	7	92	7	105	7
7	99	14	72	21	86	17	79	7	40	9	58	7
8	188	20	88	11	122	13	170	12	72	6	109	8
9	180	14	126	10	149	11	156	9	123	8	140	7
10	141	20	44	13	95	13	116	17	55	11	7[illegible]	12
Mean	155 9		97 0		119 7		121 8		75 9		96 1	

fell by an average of 20 per cent of the waking pressure and were significantly less variable than during waking During sleep systolic pressure was still significantly more variable than diastolic pressures

Spontaneous fluctuations of pressure occurred approximately every 90 to 120 minutes during sleep (Fig 5) and accounted for the greatest variability during this period being probably due to periods of rapid eye movement (REM) sleep An alternative explanation for this rhythmicity could be that these fluctuations reflect the

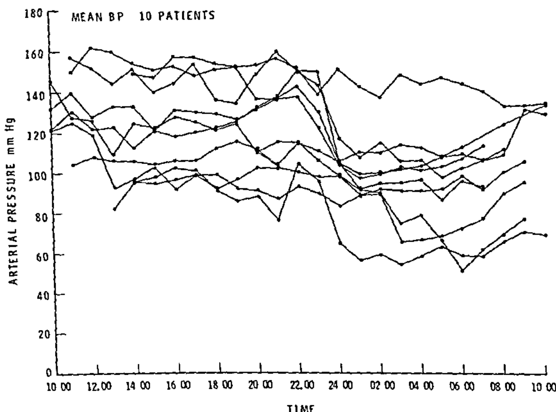


Fig 3 A plot of mean arterial pressure (diastolic pressure plus a third of the pul e amplitude) for ten patients This emphasizes the fall in arterial pressure during sleep in all but one subject (Case 10) and this individual did not sleep very well during the period of study which is refle ted in the arterial pressure which was maintained at a similar level to that during waking

changes in arterial pressure produced by respiration

Discussion

The development of systems for continuously recording arterial pressure has enabled us to obtain a more accurate characterization of an individual s blood pressure during his normal daily activities and thus avoid the pitfalls that may occur due to the presence of the orientating or defence reflex The automatic analysis system makes it possible to measure each individual beat during the 24 hour period and obtain quantitative data useful in the assessment of hypotensive therapy The results in a group of patients studied before and after beta blockade will form the basis of a separate publication Since sleep produces similar percentage falls in pressure irrespective of the over all level in arterial pressure it is perhaps not surprising that drug therapy which lowers blood pressure does not apparently alter this bi modality [7] Patients who did not sleep very well or at all did not demonstrate this bi modality

Systolic pressure shows much more variation during the day and night when compared with diastolic pressure and the higher the level of systolic pressure the greater was the variability This may reflect the poorer baroreflex control found in hypertension [8] Sokolow and associates [9] using frequent semiautomatic blood pressure recordings taken by the ambulatory patient away from the medical environment have shown that although the prevalence of hypertensive compli cations increases as the casual pressure increases the portable diastolic pressure tends to be more predictive of severity class than does the casual diastolic pressure Whether or not the variations in systolic pressure are of themselves important in determining the degree of target organ damage cannot be answered by the present study and will

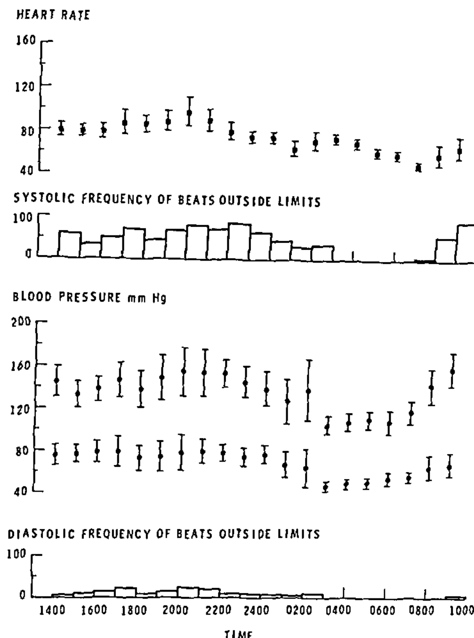


Fig 4 A plot of systolic and diastolic pressure against time in an individual patient Pressures have been averaged for each hour and plotted with its standard deviation Note that during waking the pressure is higher and more variable (as indicated by the larger standard deviations) than during sleep In addition in this diagram the frequency of those beats above the arbitrary limits of 140 systolic and 90 diastolic have also been plotted

require longitudinal studies on the same patient over a large number of years A recent report of the Framingham Study[10] appears to confirm the importance of systolic hypertension as a risk factor in cardiovascular disease—systolic pressure being a stronger determinant for the risk of coronary heart disease than either diastolic or mean blood pressure in women and in men over 45 years of age It appeared to be independent of other variables and to retain its importance when subjects with other risk factors for coronary artery disease were excluded from analysis Kannel[10] has suggested that systolic hypertension may accelerate atherogenesis or may reflect an increased susceptibility to atherogenesis due to an altered state of the arterial wall while Page and Sidd[11] have suggested an alternative explanation that is that it may simply reflect advancing atherogenesis in the absence of other known risk factors

We have found that the casual blood pressures measured in outpatient clinics tended to be higher than the average 24 hour pressure recorded by our method in some 60 per cent of patients This is not surprising since our average 24 hour figure would include the period while the patient was

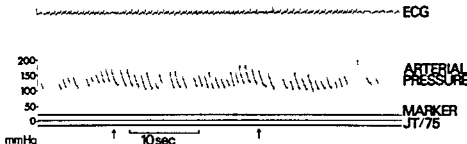


Fig 5 A record from a young woman (Case 6) obtained during sleep It shows both the electrocardiogram and the arterial pressure There are marked spontaneous increases in arterial pressure occurring in rhythmic fashion during this period of sleep Note the marked slowing associated with this rise in pressure (This pattern we believe is an example of baroreflex activity during sleep buffering an initial sympathetically mediated rise in blood pressure)

asleep and exclude the alerting response to an observer whereas casual recordings are invariably taken during the waking period which necessitate the presence of an observer This finding has been shown on several occasions previously Furthermore Sokolow and colleagues[9] found that the presence of target organ damage related more closely to the average pressure for the 24 hours than to the casual blood pressure We have not attempted such a comparison in our small group of patients reported here but in a previous publication we have shown that the averaged 24 hour blood pressure in patients with high casual levels and little evidence of target organ damage was significantly lower than the average casual readings over several months and furthermore indicated the use of this type of assessment in patients who are difficult to diagnose because of the great variability of their arterial pressure

Summary

Direct arterial pressure has been recorded continuously on magnetic tape in totally unrestricted patients going about their normal routine outside hospital for periods of 24 hours

On replaying these tapes data are derived in digital form of systolic diastolic and mean pressure plus pulse interval all on a beat by beat basis a computer program then performs averaging and statistical analysis of these data

The frequency distribution of blood pressure over a 24 hour period was plotted and showed a bi modal curve the lesser mode being due predominantly to sleep This bimodality was unaffected by the average 24 hour pressure but was modified by the length of sleep

The variability of arterial pressure was determined from the standard deviation by averaging pressure over each hour in 10 patients (five men five women) They were selected to give a range of different levels of arterial pressure and had never received drugs Throughout the 24 hours the variability of systolic pressure was significantly greater than that in diastolic pressure This variability was most acutely affected by physical exercise

During sleep both systolic and diastolic pressure fell by an average of 20 per cent of the waking pressure and both were less variable than during waking Spontaneous rhythmic changes of pressure occurring approximately every 90 to 120 minutes accounted for the greatest variability during sleep and were probably due to REM sleep

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The systolic time intervals in thyroid dysfunction

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Cardiovascular changes in thyroid disease are a well known fact since thyroid hormones have a positive chronotropic and inotropic action. Heart rate, maximum velocity of fiber shortening, rate of rise of left ventricular pressure (LV dp/dt), and cardiac output are therefore increased in patients with hyperthyroidism. In hypothyroidism all these parameters are reduced.[4] Non-invasive techniques such as the systolic time intervals (STI) allow us to assess myocardial contractility because they correlate with LVdp/dt and stroke volume. The time intervals can easily be obtained by simultaneous recording of the electrocardiogram (ECG), carotid pulse tracing, and phonocardiogram. Being inexpensive and carrying no risks, the investigation can be performed repeatedly and yields immediate results.

The purpose of this study was to investigate the value of the STI in the diagnosis of hyper- and hypothyroidism and to evaluate the correlation between thyroid function and STI.

Furthermore, we assessed the value of the STI as a follow-up examination during treatment of thyroid dysfunction.

Finally, the accuracy of another frequently used non-invasive test, namely the Achilles reflex time, was compared with that of the STI.

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Methods

Patient selection. Between June 1974 and June 1975, 53 patients (34 women and 19 men with a mean age of 44 ± 17 years, range 19 to 80 years) with signs or symptoms suggesting thyroid dysfunction were investigated and thyroid function tests as well as 75 STI were obtained. Patients with congestive heart failure, arterial hypertension, atrial fibrillation or flutter, old myocardial infarction, or abnormal cardiac findings in their chest x-ray were excluded from the study. None of the patients received cardioactive drugs such as digitalis, β-adrenergic blocking agents, or other medications with possible effects on myocardial contractility or peripheral resistance.

The complete endocrine investigation disclosed 17 patients with hyperthyroidism before treatment (10 patients with toxic diffuse goiter (Grave's disease), four with toxic uninodular goiter, two with toxic multinodular goiter, and one patient with exogenous thyroid hormone excess). Eight subjects had primary hypothyroidism. In 15 cases a euthyroid state was proven.

Four hyperthyroid patients were followed one or several times during treatment with carbimazole and three hypothyroid patients were followed during substitution with increasing doses of thyroid hormones.

Thyroid studies. On the basis of two or more thyroid tests and response to treatment we made a classification into seven groups (see Table I).

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Table I Laboratory values for serum thyroxin (T_4) and free T_4 Index (FT_4I) in the different groups of patients, excluding patients with isolated T_3 hyperthyroidism

	T (µg/100 ml) (mean ± 1 SD)	FT I† (mean ± 1 SD)
Group 1 (n = 13)	8 9 ± 1 8	8 7 ± 1 9
Group 2 (n = 8)	22 6 ± 6 6	33 9 ± 12 8
Group 3 (n = 7)	20 3 ± 4 5	23 1 ± 6 8
Group 4 (n = 13)	8 8 ± 3 1	8 1 ± 3 1
Group 5 (n = 3)	2 4 ± 1 8	3 3 ± 2 3
Group 6 (n = 7)	3 5 ± 1 2	3 5 ± 1 4
Group 7 (n = 12)	9 2 ± 2 4	8 8 ± 2 4

Normal values for T = 5 to 12 µg/100 ml
†Normal values for FT I = 4 0 to 15 4

Patients could reappear in another group after treatment

1 Euthyroid (n = 15)

Serum thyroxine (modification of Murphy and Pattee[1]) and free T_4 Index (FT_4I) within normal range

Normal T_3 (radioimmunoassay modification of Hesch and Evered[9])

Normal TRH stimulation test* (according to Staub and associates[11])

These patients served as normal controls Their STI were comparable to the normal values published by Weissler and colleagues

2 Hyperthyroid without treatment (n = 11)

Elevated serum thyroxine and FT_4I

and/or elevated T_3

and/or abnormal TRH test (delta TSH < 2 0 µU/ml)†

3 Still hyperthyroid on treatment (n = 7)

Elevated serum thyroxine and FT_4I

and/or elevated T_3 with suppressed TSH after TRH

4 Previous hyperthyroidism euthyroid on treatment (n = 13)

Normal serum thyroxine and FT_4I

and normal T_3

and/or normal TRH test (this test was evaluated only if TSH could be stimulated)

5 Hypothyroid without treatment (n = 4)

Reduced serum thyroxine and FT_4I

and abnormal TRH test (elevated basal TSH and/or exaggerated response to TRH)

6 Still hypothyroid on treatment (n = 11)

Abnormal TRH test (elevated basal TSH and/or exaggerated response to TRH)

7 Previous primary hypothyroidism euthyroid on treatment (n = 14)

Normal TRH test*

Systolic time intervals (STI) The systolic time intervals were measured in supine position at least 2 hours postprandially after a 10 minute period of rest Electrocardiogram (Lead II) phonocardiogram and carotid pulse tracing were recorded simultaneously on a Hellige six channel recorder (multiscriptor 9400/6) with a paper speed of 100 mm/sec The following intervals were measured directly

a *Left ventricular ejection time (LVET)* as the interval between the beginning of the initial upstroke and the trough of the incisural notch of the carotid pulse tracing

b The total electromechanical systole (Q S) as the interval between the beginning of the Q wave in the electrocardiogram and the first high frequency vibration of the aortic component of the second heart sound

From the above measurements the preejection period (PEP) was calculated by subtracting LVET from Q S

The isovolumic contraction time was not measured because of difficulties in clearly delineating the beginning of the first heart sound in several instances

The values for LVET and PEP were corrected for a hypothetic heart rate of zero using the regression equations of Weissler and associates and then designated with the subscript c

In all patients the ratio LVET /PEP_c was calculated In 33 patients, the Achilles reflex time and PEP were determined simultaneously to permit comparison

For the statistical analyses the Student s t test was used The correlations were calculated and plotted with a Hewlett Packard computer

All data are reported as mean ± 1 SD

Results

1 STI in patients with hyperthyroidism In patients with hyperthyroidism (untreated or on treatment Groups 2 and 3) PEP_c was shortened significantly (89 8 ± 12 3 msec and 94 7 ± 8 3 msec respectively compared to a control of 118 0 ± 9 3 msec ($p < 0\,0005$) see Fig 1) Although to a lesser degree this was also true for

* A normal TRH test rules out any form of hyper or hypothyroidism
†TSH after stimulation with TRH is equally suppressed in patients with mild and severe hyperthyroidism

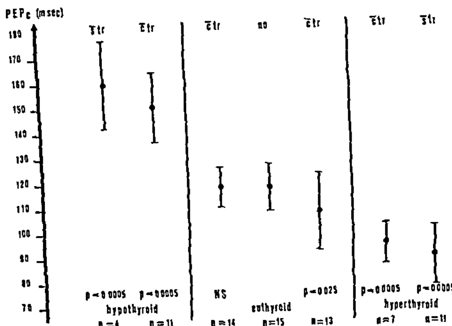


Fig 1 The corrected pre-ejection period (PEP) shows a significant prolongation in hypothyroid patients but is shortened in hyperthyroidism Patients with successfully treated hyperthyroidism (euthyroid on treatment) had still a somewhat shortened PEP p values represent significance of the patient group when compared with the group of normal controls (*no*) *NS = not* significant *x̄tr* = without treatment *ctr* = on treatment

patients with previous hyperthyroidism (Group 4 PEP = 107 7 ± 14 8 msec) LVET was only slightly and insignificantly prolonged (Fig 2)

There was a significant increase in the ratio of LVET /PEP in patients with hyperthyroidism (4 71 ± 0 69 and 4 42 ± 0 41 for Groups 2 and 3 respectively compared to a control of 3 52 ± 0 31 p < 0 0005) To a smaller degree this occurred in patients with successfully treated hyperthyroidism (3 95 ± 0 63 Fig 3)

2 STI in patients with hypothyroidism In hypothyroid patients (untreated or on treatment Groups 5 and 6) PEP was prolonged significantly (159 8 ± 17 4 msec and 149 7 ± 14 1 msec respectively) in comparison with the control group (p < 0 0005) The LVET was shortened (398 4 ± 14 3 msec and 400 1 ± 14 5 msec respectively see Figs 1 and 2) The ratio LVET /PEP was therefore significantly decreased in patients with hypothyroidism (2.52 ± 0 35 and 2 7 ± 0 3 respectively (p < 0 0005) Fig 3) Euthyroid patients with previous hypothyroidism did not differ from the controls (Figs 1 to 3)

3 Correlation between thyroid function tests and STI A significant linear correlation (r = −0 67 p < 0 001) between PEP and T (Fig 4) as well as between LVET /PEP and T₄ (r = 0 64 p < 0 001 Fig 5) was found

The correlation between PEP and FT I (r = −0 58) followed an exponential curve The same was noted with the correlation LVET / PEP and FT I (r = 0 58) If plotted in a semilogarithmic way the correlation between these two parameters and FT I improved (r = −0 68 r = 0 66 respectively p < 0 001) and seems to be linear The semilogarithmic plotting of the correlation between PEP and FT I is shown in Fig 6

4 Serial studies in patients with thyroid dysfunction In seven patients (three with hypothyroidism and four with hyperthyroidism) serial determinations of both STI and thyroid function tests were done As shown in Fig 7 abnormal PEP values returned to normal during treatment of thyroid dysfunction in five of seven patients while the other two showed a tendency to return towards normal This documents the value of serial determinations of PEP during treatment

5 The Achilles reflex time compared with the PEP in the assessment of thyroid dysfunction In 33 patients 46 measurements of both Achilles

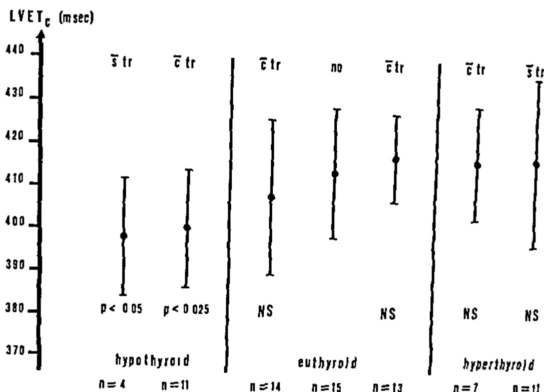


Fig 2 The corrected left ventricular ejection time (*LVET*) is not significantly altered in hyperthyroidism but shows a tendency to shorten in hypothyroidism p values represent significance of the patient group compared with the group of normal controls (*no*) *NS* = not significant *s̄tr* = without treatment *c̄tr* = on treatment

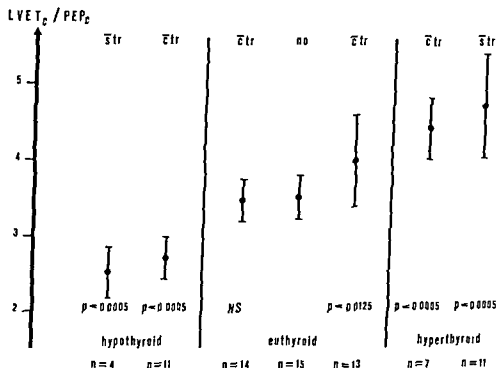


Fig 3 The ratio LVET /PEP reveals a significant shortening in patients with hypothyroidism but is increased in hyperthyroidism p values represent significance of the patient group compared with the group of normal controls (*no*) *NS* = not significant *s̄tr* = without treatment *c̄tr* = on treatment

reflex time and PEP were performed simultaneously The determination of PEP permitted a better classification of patients with thyroid dysfunction This was mainly due to a wide range of Achilles reflex times Patients with untreated hyperthyroidism revealed no significant change in Achilles reflex time in comparison with normal controls (Fig 8 Table II)

Discussion

In this study of 17 patients with hyperthyroidism (18 determinations) there was a signifi

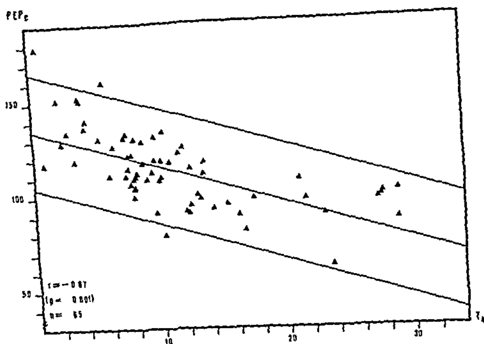


Fig 4 In this figure the correlation between PEP and T is depicted $n = 65$ $r = -0.67$ ($p < 0.001$)

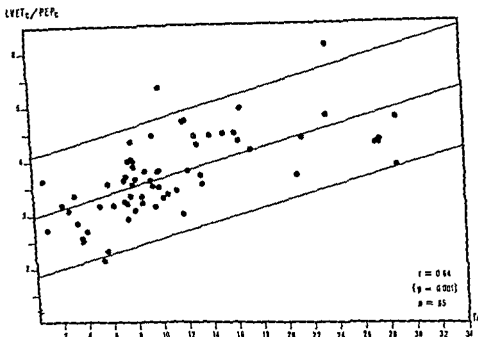


Fig 5 The graph shows the correlation between LVET /PEP and T

cant shortening of PEP documenting an enhanced myocardial contractility caused by thyroid hormones The LVET was not significantly altered in this group In eight patients with hypothyroidism (15 determinations) PEP was prolonged due to a decreased myocardial contractility The shortening of LVET suggests a fall in stroke volume These results confirm the findings of other authors who found a shortening of PEP in hyperthyroid patients[21,23] and a prolongation of PEP as well as a shortening of LVET in hypothyroid patients[2]

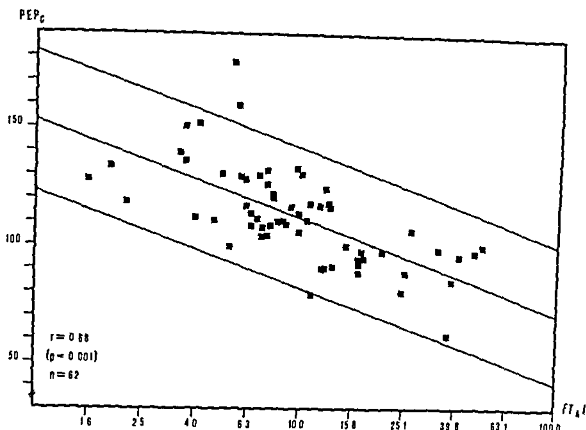


Fig 6 The correlation between PEP and the free T Index (FT I) is linear if the FT values are plotted in a logarithmic way

In all but one of our patients with thyroid dysfunction PEP differed at least 1 SD from the mean of our control values In 25 patients it differed by 2 SD or more This means that even if one applies 2 SD (Fig 9), thyroid function can be evaluated correctly in approximately 75 per cent of patients

Since thyroid function did affect the $LVET_c$ less than PEP_c the determination of PEP alone was more helpful in assessing thyroid function than the calculation of the ratio $LVET_c/PEP_c$

The sensitivity of the method is further documented by the change in PEP observed in patients with thyroid dysfunction on treatment (Fig 1)

In two patients with isolated T_3 hyperthyroidism the PEP values were shortened by more than 2 SD below our normal values suggesting the usefulness of PEP in the confirmation or detection of this unusual form of thyrotoxicosis Hence, we feel that in the case of a normal T_4 and a shortened PEP T_3 levels should be determined

Serial measurements of PEP during the treatment of thyroid dysfunction were particularly helpful Five out of seven patients with abnormal thyroid function in whom serial determinations of PEP_c were performed showed a normalization of this time interval after successful treatment In the other two patients there was a change towards normal (Fig 7)

In our experience the Achilles reflex time is of little help in hyperthyroid patients where PEP is the most valuable parameter Patients with hypothyroidism may be evaluated by both methods PEP_c again being better related to thyroid dysfunction (Fig 8)

The influence of thyroid hormones on the STI is further documented by the correlation between thyroid function and PEP as well as the ratio LVET /PEP The correlation between T_4 and PEP and T_4 and LVET /PEP seems to be linear (Figs 4 and 5) If the FT_4I was chosen instead of T_4 the correlation between these parameters was linear only if plotted in a semilogarithmic way (Fig 6) This correlation may be explained by a maximum enhancement of myocardial contractility in patients with severe hyperthyroidism These patients show excessive values of the free thyroid hormone not bound to the carrier protein thyroid binding globulin (TBG) The free hormone is the only metabolically active form of

Table II Achilles reflex time compared with PEP in thyroid dysfunction

	ASR ± 1 SD (msec)	PEP ± 1 S.D
Group 1	[illegible]4 ± 45 1 (n = 8)	119 4 ± 6 4 (n = 8)
Group 2	26[illegible] 8 ± 86 7 (n = 6) NS	84[illegible] ± 14 3 (n = 6) p < 0 0005
Group 3	234 [illegible] ± 2[illegible] 9 (n = [illegible]) p < 0 0[illegible]5	93.2 ± 9 7 (n = 5) p < 0 0005
Group 4	[illegible]03.5 ± 33 2 (n = 9) NS	108 4 ± 16 9 (n = 9) NS
Group 5	4[illegible]4 6 ± 134 9 (n = 4) p < 0 01	160 0 ± [illegible] (n = 4) p < 0 0005
Group 6	3 90 ± 6[illegible] 8 (n = 5) p < 0 005	153 4 ± 16 5 (n = [illegible]) p < 0 0005
Group 7	290 8 ± 39 9 (n = 9) NS	117 9 ± 8 8 (n = 9) NS

Γ The latter is more accurately correlated to the FT I than to the T value which mainly measures the bound fraction

The recent development of new biochemical procedures for investigation of thyroid dysfunction (radioimmunoassays for T_3 and TSH as well as the TRH test) allows the detection of minor degrees of thyroid dysfunction in very early stages (preclinical hyper and hypothyroidism) In some cases these tests are too sensitive and their clinical significance can be disputed (e g elevated levels of TSH or thyroid hormones in euthyroid subjects * or hyperthyroidism with normal values for T and FT I *)

In the meantime we have seen 12 patients in whom one of the laboratory parameters of thyroid function was abnormal but who had no clinical evidence for thyroid dysfunction In all of these patients the systolic time intervals were within normal limits We feel that in such cases the systolic time intervals may be of help in the clinical evaluation of thyroid function

The usefulness of this noninvasive test is furthermore stressed by advantages such as immediate availability easy repetition and safety However in patients with intrinsic heart disease in addition to hypothyroidism PEP

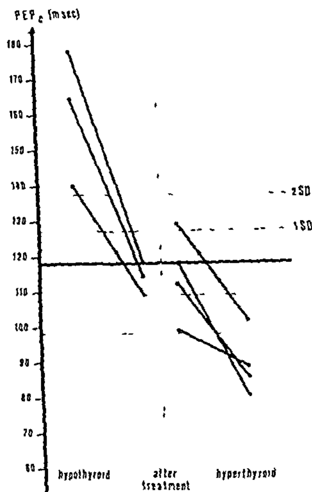


Fig 7 In five of seven patients with thyroid dysfunction in whom serial studies of PEP were done this time interval returned to the normal range (± 1 S D) after successful treatment

would be expected to be prolonged out of proportion for their hypothyroid state alone A further practical drawback lies in the fact that STI are of no help in patients receiving β blocking agents for hyperthyroidism

Summary

The systolic time intervals (LVET PEP and ratio LVET/PEP) were determined in 53 patients presenting with signs or symptoms of thyroid dysfunction Patients with clinical evidence for congestive heart failure with arterial hypertension or old myocardial infarction and patients receiving cardioactive drugs were excluded from the study Thyroid function was evaluated by means of T RIA serum thyroxin and TRH stimulation test

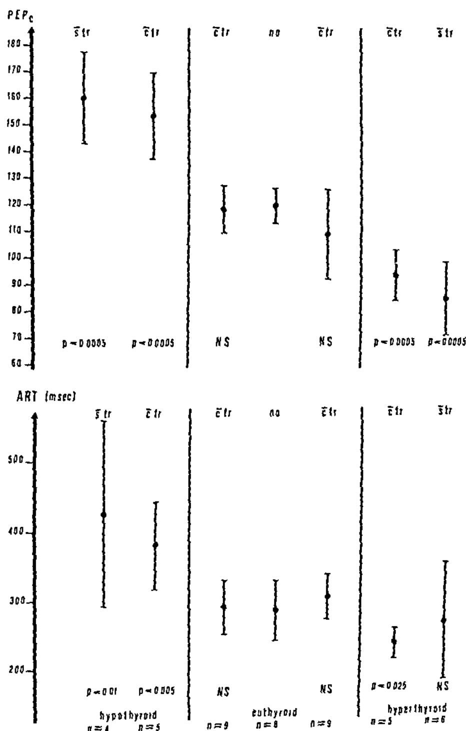


Fig 8 This figure compares the usefulness of PEP and the Achilles tendon reflex time (ART) in the assessment of thyroid dysfunction The determination of PEP permits a better classification than the ART p values represent difference between the patient group and the normal controls

In patients with hyperthyroidism (untreated and on treatment) PEP was shortened significantly (91 7 ± 11 0 msec compared to a control of 118 ± 9 3 msec) LVET was prolonged only insignificantly Hence the ratio LVET /PEP$_c$ showed a significant increase in hyperthyroid patients

In hypothyroid patients (untreated and on treatment) PEP$_c$ was prolonged to 152 4 ± 15 1 msec LVET$_c$ was shortened (399 7 ± 14 4 msec compared to a control of 413 7 ± 15 9 msec) The ratio LVET$_c$/PEP$_c$ was decreased In seven patients, serial determinations of PEP$_c$ were performed the values returned towards normal after successful treatment of thyroid dysfunction

A significant linear correlation between PEP and T$_4$ (r = −0 67) as well as LVET /PEP$_c$ and T$_4$ (r = 0 64) was found In 17 patients with hyperthyroidism and in eight patients with hypo

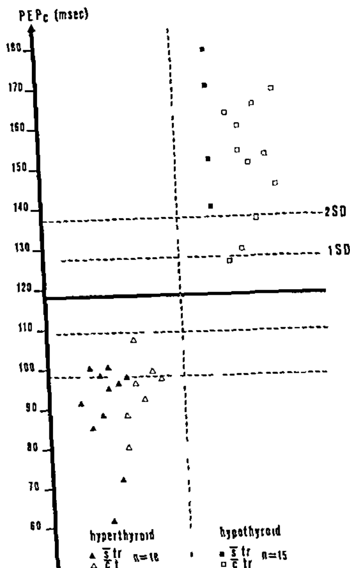


Fig 9 PEP values of 18 patients with hyper and 15 patients with hypothyroidism are shown in this figure Thirty two of 33 PEP values of these patients with thyroid dysfunction were outside the normal range (± 1 SD)

thyroidism 33 determinations of PEP were performed All but one of the values differed by at least 1 SD from our normal group or taking 2 SD thyroid function could be evaluated correctly in approximately 75 per cent of patients

We wish to thank J Girard M D for the performance of the TSH assays. Furthermore the authors gratefully acknowledge the helpful comments of Prof G M Besser St Bartholomew s Hospital London

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The effects of psychological stress and vagal stimulation with morphine on vulnerability to ventricular fibrillation (VF) in the conscious dog*

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Recent studies have emphasized the importance of neural and psychological factors in the occurrence of sudden death [1] In the experimental animal diverse psychologic stresses lower the vulnerable period threshold for ventricular fibrillation [2] In man psychologic stresses have been associated with the occurrence of arrhythmias and the precipitation of sudden death These stresses are mediated largely through the sympathetic limb of the autonomic nervous system Enhanced sympathetic neural tone whether resulting from subcortical [11] hypothalamic or stellate ganglion stimulation or whether the consequence of catecholamine administration predisposes to ventricular fibrillation In contrast increased vagus nerve activity whether by electrical or pharmacologic means exerts a protective effect against ventricular fibrillation when sympathetic tone is augmented

These observations suggest that drugs which alter psychologically initiated neural inputs to the heart will diminish susceptibility to ventricular fibrillation In modeling such experiments in animals one is confronted by methodologic difficulties The study of vulnerability in the conscious state using VF as an endpoint is complicated by two considerations Firstly it is inhumane to subject animals repeatedly to the high currents necessary to provoke VF and the high electrical energies required to terminate this arrhythmia Secondly resuscitative efforts alter autonomic tone and induce trauma vitiating meaningful investigation of psychologic variables These methodologic difficulties may be surmounted by utilizing the repetitive extrasystole (RE) as an endpoint rather than VF Matta and associates[1] have demonstrated that there is concordance between the threshold currents required to elicit VF and RE About 66 per cent of the current required to induce VF will consistently result in a repetitive response The nadirs of threshold for both VF and RE are coincident in the cardiac cycle Furthermore during interventions such as electrical stimulation of the vagus and stellate ganglia catecholamine infusion and beta adrenergic blockade identical shifts occur in these two periods within the cardiac cycle

In the present study RE threshold was employed to determine the effects of morphine sulfate on cardiac vulnerability in the psychologically stressed animal This drug is widely used to allay anxiety and pain during the inception of an acute cardiac ischemic episode at a time when there is marked susceptibility to VF However no information exists on the action of morphine on ventricular vulnerability in the awake animal

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The purpose of this study was twofold (1) to investigate the time course of changes in vulnerability associated with psychological stress and (2) to determine if morphine alters the response to stress, and if so, to define the mechanism(s) of its actions

Material and methods

Surgical procedures Twelve healthy adult mongrel dogs of either sex weighing 9 0 to 15 0 kilograms were selected for study All dogs were tested and were found to be free from heart worms (*Dirofilaria immitis*) Seven days prior to the definitive investigation the animals were anesthetized with intravenous methohexital (10 mg /Kg) A recording catheter (Elecath 003992) and a bipolar pacing catheter (Medtronic 6901, interelectrode distance 28 mm) were positioned in the right ventricle via a jugular vein as previously described [16, 17] The tip of the pacing catheter was wedged firmly in the apex of the right ventricle A blood pressure catheter was passed retrograde into the aorta through an omocervical artery and flushed with concentrated heparin All catheters were exteriorized at the nape of the neck Mean arterial blood pressure was measured by electrically integrating the pulsatile output of a Statham 23dB pressure transducer

Electrical testing of the heart Ventricular vulnerability to fibrillation was assessed by the repetitive extrasystole (RE) threshold method [18] A Medtronic battery powered pacemaker provided rectangular 2 msec pulses at 273 msec intervals This rate (220 beats/minute) was necessary to override tachycardia in the stressful environment and following atropine administration The distal pole was made cathodal and the pacemaker output was adjusted to twice the mid diastolic threshold A special purpose constant-current pulse generator with an electrically isolated output provided test stimuli of 5 msec duration It was equipped with circuitry to inhibit the pacemaker output for 3 seconds immediately following the test stimulus The vulnerable period threshold was determined as follows with heart rate maintained at 220 beats/minute scanning for the RE threshold was commenced with a stimulus intensity of twice the mid diastolic threshold starting 30 msec beyond the refractory period The test stimulus was delivered progressively earlier by 5 msec intervals until the refractory period was encountered If no RE resulted the stimulus intensity was increased by 2 ma and the scanning procedure was repeated The RE threshold was taken to be the minimum current intensity at which RE occurred in two out of three trials This method provided a more rapid assessment of the vulnerable period threshold than sequential R/T pulsing utilized in previous studies [8, 10]

Ventricular fibrillation was rare with this method When it occurred, defibrillation was accomplished within 60 seconds The study was then discontinued and the animal was tested the following day

Psychologic environments The animals were studied in two environments as previously described [8, 9] The nonstressful environment consisted of a large cage in a sound attenuated room A counterbalanced cable suspended from the top of the cage contained connections for the cardiac and blood pressure catheters This permitted the animal to move freely within the cage The animals appeared relaxed and after a few minutes were lying down quietly

The stressful environment consisted of a Pavlovian sling in which the animal was restrained and movement was limited Cables were connected to the cardiac catheters so that a continuous oscilloscopic display of the ECG was obtained and pacing and test stimuli could be delivered A single 5 wsec shock from a cardioverter was delivered via copper plates (80 cm^2) fastened across the thorax The dog remained in the sling for 10 minutes before the synchronized transthoracic shock was administered and for 10 minutes following the shock

Experimental protocol The psychological conditioning protocol was as follows six dogs were exposed first to the sling environment and then to the cage setting In the remaining six dogs the sequence was reversed

All animals were exposed to both environments on three consecutive days prior to cardiac testing A 5 wsec transthoracic shock was administered in the sling on each of these days No further shocks were administered after the third day This conditioning period was selected based on earlier experiments which showed that maximal effects on RE threshold are evident after this period [8] Measurement of heart rate arterial blood pressure and RE threshold was commenced on the fourth day These determinations were carried out after the

Table I Summary of experimental protocol

Day	*Experimental procedure*
1 3	Aversive conditioning in sling followed by placement in cage Placement in cage followed by aversive conditioning in sling
4	Electrical testing for RE threshold in cag and sling environments
5	Administration of MS in sling environment Administration of atropine following MS (6 dogs)
6	Non study day to allow dissipation of morphine
7	Electrical testing for RE threshold in cage and sling environments Administration of MS in cage environment
8	Study of time-course of recovery in RE threshold in cage

animal had been in the cage environment for one hour and when in the sling for 10 minutes The six dogs in the sling to cage paradigm were studied again on the eighth day In these dogs RE threshold heart rate and blood pressure measurements were made at 10 minutes in the sling Additional measurements were made at 10 30 50 and 70 minutes in the cage Morphine sulfate (0 25 mg /Kg) was injected intravenously on the fifth day of study 30 minutes before placing the dogs in the sling environment After determining the effect of MS on heart rate arterial blood pressure and repetitive extrasystole threshold atropine sulfate (0 2 mg /Kg intravenously) was given to six dogs Threshold determinations were made within 15 minutes after administration of atropine One day was allowed for drug dissipation and on the seventh day repetitive extrasystole thresholds were redetermined to assess the presence of the effect of aversive conditioning In the six dogs which had been exposed to the sling to cage paradigm morphine sulfate (0 25 mg / Kg) was given in the cage setting to determine the influence of the drug in the absence of aversive stimuli A summary of the protocol is shown in Table I

Results were analyzed using Student s t test for paired data The criterion of significance was $P < 0.05$

Results

Influence of psychological environment on ventricular vulnerability The animals exhibited different behavioral responses after three days of conditioning in the two environments The dogs entered the nonstressful cage voluntarily and usually lay down within a few minutes In contrast entry into the sling environment was resisted In the sling animals exhibited increased muscular tone somatic tremor and occasionally there was loss of sphincter control Heart rate increased from 102 ± 5 to 134 ± 3 beats/minute ($P < 0.01$) and arterial blood pressure rose from 84 ± 6 to 120 ± 5 mm Hg ($P < 0.01$) The RE threshold for all 12 dogs was 45 per cent lower in the sling as compared to the cage ($P < 0.01$) (Tables II and III) The sequence with which the animals were placed in the two settings did not appear to affect the changes in the above determinations

Time course of changes in ventricular vulnerability In six animals significant reduction in RE threshold and increase in heart rate and blood pressure occurred within 10 minutes after being

Table II Effect of repetitive extrasystole (RE) threshold in dogs placed first in a nonaversive cage setting followed by an aversive sling environment The influence of morphine sulfate (MS) (0 25 mg /Kg) was determined on day 5 N = 6 dogs

Day of study	RE threshold (ma)		P
	Cage	Sling	
4	37 ± 5†	18 ± 2	< 0 01
5	28 ± 4	(MS)21 ± 2	< 0 01
7	27 ± 3	20 ± 2	< 0 01
	NS	P < 0 001	

†Values are means ± SEM
Ref rs to statistical comparisons between sl g and cage
Ref rs t statisti al comparisons between MS-t eated and control anim ls.

Table III Effect on RE threshold of placing dogs first in sling and then in cage N = 6 dogs

Day of study	RE threshold (ma)		P
	Sling	Cage	
4	17 ± 4‡	31 ± 5	< 0 01
5	(MS)25 ± 4	—†	—
7	13 ± 4	28 ± 4	< 0 01
	P < 0 02	NS	

Refers t statisti al compariso s between sling and c ge
Refers to st tistical comparisons between MS treated and c trol nim ls.
†V lu not obta ned due to prior dministration of MS in l ng en ro ment
‡Val es are means ± SEM

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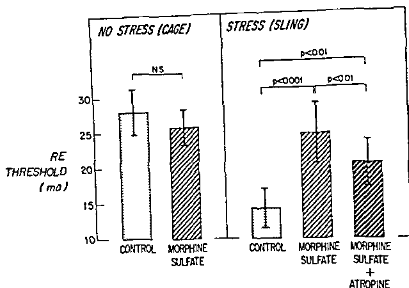


Fig 3 Effect of morphine sulfate (MS) on RE threshold in the two environments Morphine (0.25 mg/Kg) significantly elevated RE threshold in the sling environment by 40 per cent ($p < 0.001$) Administration of atropine sulfate (0.2 mg/Kg) following MS partially annulled this effect but RE threshold still remained significantly above the control level in the sling ($p < 0.01$) MS was without effect on RE threshold in the cage environment

was 81 ± 4 mm Hg in the control state and 87 ± 7 mm Hg following morphine

Discussion

The cardiovascular response to psychological stress is a complex composite of several adaptive processes representing an integrated pattern of interactions between the higher cortical centers hypothalamus and medullary vasomotor centers Perception of a stressful environment results in neural and humoral changes provoking alterations in autonomic function with catecholamine and adrenocortical hormone release This cortico-hypothalamic reaction is reflected in somatomotor alterations manifest in part by an increase in blood pressure marked inotropic and chronotropic effects on the heart and increase in muscle tone [3] The cardiovascular response to stress involves both vagal inhibition and sympathetic stimulation [5] To date the focus of study of the cardiovascular response to higher neural and psychologic inputs has involved hemodynamic effects. Little attention has been given to heart rhythm alterations That substantial changes may be elicited is indicated by recent findings that stimulation of the posterior hypothalamus results in a 40 per cent reduction in VF threshold In animals with acute myocardial ischemia electric stimuli to the hypothalamus induce ventricular fibrillation In the conscious state psychological stress reduces the vulnerable period threshold by 50 per cent [1]

In the present study restraining the animals in an aversive environment consistently evoked marked increases in ventricular vulnerability in heart rate and in blood pressure This response to stress was not extinguished for five days after cessation of the painful stimulus In the cage to sling paradigm a 45 per cent reduction in the vulnerable period threshold occurred within ten minutes of placement in the stressful environment This observation demonstrates that psychologic stress can alter cardiac vulnerability rapidly and profoundly Reversing the cage-sling sequence did not alter the magnitude of change in vulnerability Shifting animals from the aversive sling to the tranquil cage environment permitted determination of the temporal sequence in RE threshold recovery occurring with relaxation The immediate response was a slowing in heart rate and a decrease in blood pressure These changes were significant and suggest a lessening of sympathetic activity on the heart and vasculature However it is noteworthy that these initial alterations were not accompanied by recovery in vulnerability There was a striking lag in recovery

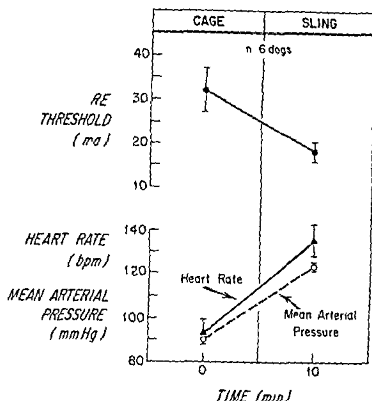


Fig 1 Effect of aversive sling environment on repetitive extrasystole (RE) threshold, heart rate (HR) and arterial blood pressure (BP) in six dogs. The RE threshold decreased 40 per cent within 10 minutes of placing the animals in the sling after removal from the cage. This reduction in threshold was accompanied by significant elevations in heart rate and BP. Values are means ± SEM.

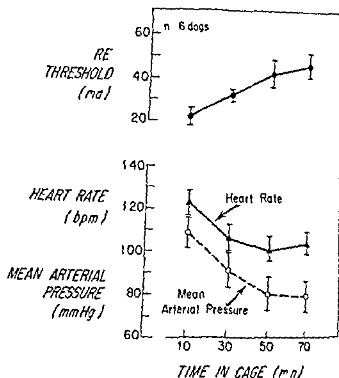


Fig 2 Effect of nonaversive cage environment on RE threshold, heart rate and arterial blood pressure in six dogs. Transferring the animals from the sling to the cage environment resulted in an increase in RE threshold which was evident after 20 minutes. The threshold continued to rise for 40 minutes thereafter. In contrast, the changes in heart rate and arterial blood pressure were evident as soon as the animals were placed in the cage; heart rate and arterial blood pressure continued to decrease over the ensuing 40 minutes.

moved from cage to sling (Fig 1). The six animals which were shifted from sling to cage exhibited no significant change in RE threshold (22 ± 2 ma vs 21 ± 2 ma) during the first 10 minutes after transfer. A significant rise in RE threshold occurred after 20 more minutes. Heart rate was 134 ± 8 beats/minute and blood pressure was 117 ± 5 mm Hg in the sling. Upon transfer to the cage significant reduction in heart rate and blood pressure occurred within the first 10 minutes ($P < 0.03$). No significant changes in RE threshold, heart rate and blood pressure occurred in the last 20 minutes in the cage (Fig 2).

Effect of MS on RE threshold in the stressful environment Administration of MS 0.25 mg/Kg 30 minutes before placing 12 animals in the sling raised RE threshold by 40 per cent ($P < 0.01$). However, RE threshold in this environment even following MS was still significantly lower than that obtained prior to exposing the animals to stress ($P < 0.01$). Heart rate was significantly lowered by morphine from 135 ± 3 to 104 ± 3 beats/minute ($P < 0.01$) and this rate was similar to that obtained in the non aversive environment. Blood pressure, however, was unchanged by treatment with morphine. Mean arterial blood pressure was 119 ± 4 mm Hg before and 115 ± 5 mm Hg after morphine administration. Atropine 0.2 mg/Kg was administered to six dogs after they had received morphine. In these animals RE threshold in the sling was 15 ± 3 ma and rose after morphine to 25 ± 4 ma ($P < 0.001$) but after atropine receded to 20 ± 3 ma ($P < 0.01$). Following atropine, RE threshold still remained significantly above that obtained before morphine administration ($P < 0.01$) (Fig 3).

Effect of MS on RE threshold in the nonstressful environment No significant change in RE threshold occurred when morphine was administered to animals while in the cage (28 ± 4 ma vs 26 ± 3 ma after morphine (Fig 3). Heart rate, however, decreased from 113 ± 8 to 100 ± 6 beats/minute ($P < 0.02$) while pressure remained unaffected. Mean arterial blood pressure

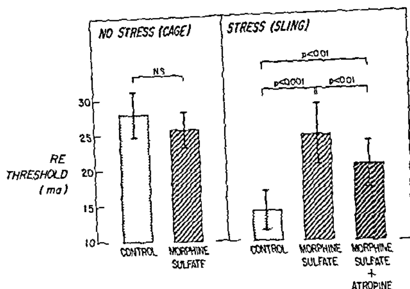


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of RE threshold toward control values which occurred in the ensuing hour associated with further decreases in heart rate and blood pressure Pretreatment with morphine altered the response to stress The increase in vulnerability was blunted by 50 per cent Under the conditions of the present experiment, the protection afforded by morphine against stress induced changes in vulnerability was less than that obtained by returning the animal to a nonstressful environment

In anesthetized dogs we have demonstrated that the vagotonic action of morphine decreases vulnerability to ventricular fibrillation [6] Vagal action on vulnerability is indirect and results from a muscarinic inhibition of sympathetic activity [16, 1] This vagal effect is predetermined by the prevailing level of sympathetic tone When sympathetic tone is high cholinergic stimulation results in a substantial elevation of the vulnerable period threshold Conversely, when adrenergic activity is low or abolished by beta adrenergic blockage, vagal stimulation is attended by insignificant changes in vulnerability [17] In the present study sympathetic stimulation was engendered by the stressful environment and the vagotonic action of morphine therefore raised the vulnerable period threshold Morphine had no effect on vulnerability in the absence of stress as no alterations on the vulnerable period threshold occurred in the nonaversive environment Vagal activation alone did not account entirely for the action of morphine on vulnerability in the conscious state Following cholinergic blockade with atropine, the vulnerable period threshold remained significantly elevated above the pre morphine level This component of morphine action may be attributed either to a direct effect on the heart or to a central action resulting in sedation and decreased sympathetic outflow A direct cardiac effect is unlikely as cholinergic blockade in the anesthetized state completely abolishes the effect of morphine on vulnerability Furthermore in the tranquil cage environment morphine was without effect These observations suggest a central action of morphine which operates significantly only in the presence of stress

Treatment with morphine induced disparate effects on heart rate and blood pressure Tachycardia was abolished in the stressful environment while blood pressure was unaffected Heart rate in the nonstressful environment was significantly reduced but blood pressure again remained unchanged The effect on heart rate may be accounted for by an indirect vagotonic action[27] as well as by a direct action of morphine on slowing the sinoatrial node [28] The effect on vulnerability was not secondary to slowing of heart rate as vulnerable period thresholds were measured at a paced rate of 220 beats/minute Increase in blood pressure during stress results largely from central sympathetic discharge resulting in vasoconstriction and increases in heart rate and myocardial contractility [3, 24] Alam and Smirk [9] have called attention to receptors in skeletal muscle which respond to strong and sustained contraction of small muscle groups Activation of these receptors excites the vasomotor centers and this results in further sympathetic outflow Morphine would tend to antagonize these effects as it causes vasodilation by the release of histamine from smooth muscle [30] However neither this effect nor the sedative and vagotonic actions of the drug were adequate in abolishing the adrenergic pressor response completely

Summary

Ventricular vulnerability to fibrillation was assessed in 12 conscious dogs in aversive and nonaversive environments using the repetitive extrasystole (RE) threshold method In the aversive environment, RE threshold was 45 per cent lower than in the nonaversive setting and heart rate and blood pressure were significantly elevated This decrease in RE threshold occurred within 10 minutes of exposing the animals to stress In contrast, the recovery in RE threshold in the nonaversive setting occurred over a 40 minute period When morphine sulfate (MS) 0 25 mg /Kg was administered to dogs in the aversive environment the RE threshold was significantly increased Cholinergic blockade of vagal efferent activity with atropine (0 2 mg /Kg) annulled partially the effect of MS on RE threshold MS was without effect in the nonaversive environment It is concluded that MS exerts a significant protective effect on increased ventricular vulnerability associated with psychological stress This effect is mediated by the vagotonic and sedative actions of morphine

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Post-extrasystolic potentiation of ischemic myocardium by atrial stimulation

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Reports of sometimes dramatic improvement in segmental left ventricular function following coronary bypass surgery although not universal [1-11] leaves the clear implication that ischemic non infarcted myocardium can exist in a state of function hibernation Afterload reducing agents[1-16] and ventricular post extrasystolic potentiation[17-19] are capable of improving segment dysfunction in man to a degree similar to that observed in the experimental animal [20-23] Since clinical studies suggest that the response to such agents is predictive of the surgical result the procedure of intervention ventriculography [16] has become widely employed during cardiac catheterization Post extrasystolic potentiation (PESP) should be the preferred stimulus in this regard since its effect is detectable during the performance of a single ventriculogram but induced ventricular extrasystoles can provoke serious sustained arrhythmias Premature atrial contractions also elicit the phenomenon of PESP [24] and are inherently safer but no data is available concerning the effects of this stimulus on regional ischemic dysfunction The present study was undertaken therefore to determine if atrial induced PESP can be used to elicit latent contractile responsiveness in acutely ischemic myocardium and to define the magnitude and duration of such responsiveness

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Methods

Studies were carried out in 11 healthy mongrel dogs weighing from 22 to 28 kilograms anesthetized with morphine sulfate (2 2 mg /Kg, intramuscular) and chloralose (100 mg /Kg, intravenous) After endotracheal intubation respiration was maintained with a Harvard ventilator A left thoracotomy was performed via the fifth inter space and the heart was suspended in a pericardial cradle The distal portion of the left anterior descending coronary artery was isolated for subsequent occlusion A 6 cm, No 10 French stiff walled Teflon catheter was inserted through the cardiac apex and secured by a purse string suture This catheter was connected via a three way stopcock directly to a BioTech transducer The frequency response of this system was determined *in vitro* by calculation[25] from the overshoot of a square wave imposed by gas flame rupture of an air filled balloon attached to the catheter tip The frequency response was 0 to 45 Hz (± 10 per cent) A 100 cm No 7 French polyethylene catheter was inserted into the thoracic aorta via the left femoral artery and attached to a Statham P23DB transducer The frequency response of this system determined as above was 0 to 20 Hz (± 10 per cent) A time delay of 50 msec was present in this system and was corrected by reference to the left ventricular tracing Pacing electrodes were applied to the right atrium via alligator clips and attached to an external fixed rate synchronous Medtronic stimulator

Left ventricular and aortic pressure were moni

tored along with Lead II of the electrocardiogram on a Honeywell multi channel ultraviolet light recorder As in previous studies from this laboratory[2, 26, 2] a 10 mm mercury in silastic length gauge (0 31 mm inner diameter 0 62 mm outer diameter)* prestressed for 30 minutes before each experiment was then sutured to the epicardial surface of the left ventricle parallel to the fibers perfused by the left anterior descending coronary artery The frequency response of this gauge determined via a mechanical oscillator is 0 to 15 Hz (± 10 per cent) The time delay is independent of frequency but varies from gauge to gauge (range 0 to 22 msec mean 15 msec) The stiffness of the gauge is 1 gr force/5 per cent elongation The length gauge was calibrated prior to use by attaching its ends to the jaws of a vernier caliper and extending the gauge by fixed increments When in use the arc of epicardium subtended by the gauge var d from 10 to 20 mm Within such a range the calibration of the gauge is not affected by variations of body temperature and is linear (± 5 per cent) for up to 8 hours

Pre extrasystolic and post extrasystolic end diastolic segment length and the magnitude of systolic shortening were measured directly from the calibrated length gauge tracing on three consecutive beats The end diastolic point was defined as the Z point of the left ventricular pressure Systolic shortening was measured as the difference between length at initial peak left ventricular pressure and length at the aortic dicrotic notch (corrected for time delay) All data were collected with the respirator turned off for 5 seconds at end expiration No drift in baseline was noted with this procedure and cyclic respiratory changes were abolished

After an initial stabilization period control data were obtained before and following interruption of normal sinus rhythm with a single synchronized atrial paced premature stimulus The mean interstimulus (R R) interval between the control and paced beat was 375 ± 7 (1 S D) msec at a mean heart rate of 102 ± 10 (1 S D) and could not be more precisely controlled due to variations in the paced PR interval The ratio of the post extrasystolic interval to the pre extrasystolic interval was 1 6 01 (1 S D) This coupling interval produced potentiation of systolic shortening on the post extrasystolic beat that

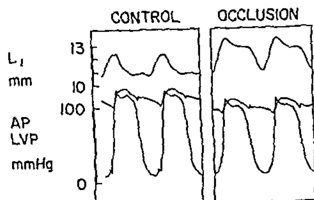


Fig 1 Effect of coronary occlusion on regional function Note the marked reduction in systolic shortening following occlusion L = length gauge LVP = left ventricular pressure AP = aortic pressure

was reproducible within 5 per cent on duplicate determination and corresponds to that used in previous studies[17] In two additional control dogs the degree of augmentation of systolic shortening remained within ± 10 per cent of control for a period of 5 hours The left anterior descending coronary artery was then ligated Data were obtained at 1 and 30 minutes following occlusion in each dog In nine dogs serial determinations were made each 30 minutes for up to 3 hours post occlusion Analysis of data for statistical significance was by the paired t test

Results

Typical control data before and after coronary occlusion is illustrated in Fig 1 Prior to coronary occlusion regional systolic shortening was 1 30 ± 0 29 mm and increased to 2 77 ± 0 42 mm on the post extrasystolic beat ($p < 0 001$) Following one minute of occlusion systolic shortening had decreased to −0 24 ± 0 06 mm ($p < 0 0001$) and in eight cases paradoxic systolic lengthening was noted but PESP improved systolic shortening in all dogs to 1 42 ± 0 24 mm ($p < 0 0001$) Thirty minutes following occlusion systolic shortening had spontaneously improved slightly to 0 32 ± 0 05 mm ($p < 0 001$) and increased to 1 14 ± 0 23 mm ($p < 0 001$) following PESP (Figs 2 and 3) Hemodynamic response at 30 minutes was typical of the total experiment Post extrasystolic left ventricular systolic pressure increased by 22 per cent from 102 ± 9 to 124 ± 15 mm Hg ($p < 0 001$) compared to the pre extrasystolic beat and aortic diastolic pressure decreased 23 per cent from 76 ± 6 to 59 ± 5

* ks Electronics, Beaverton Ore

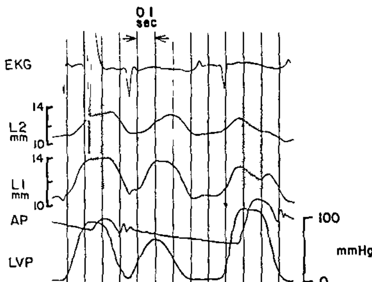


Fig 2 Early responsiveness of ischemic myocardium to post extrasystolic potentiation L represents the length gauge in the central area of ischemia and L a gauge in an adjacent area (not monitored in other experiments) The first beat represents resting (pre extrasystolic) function 30 minutes following left anterior descending coronary artery occlusion Absence of systolic shortening and slight systolic paradox is evident on both gauges *(shaded area)* The second beat represents the extrasystolic beat The third beat represents the postextrasystolic beat There is substantial improvement in systolic shortening on both length gauges End diastolic segment length and end diastolic left ventricular pressure are unchanged *AP* = aortic pressure *LVP* = left ventricular pressure

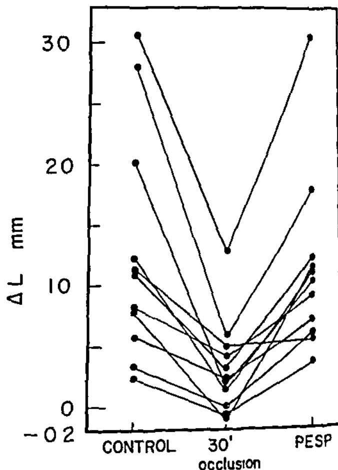


Fig 3 Post extrasystolic responsiveness of acutely ischemic myocardium Systolic shortening of the ischemic segment (ΔL) decreased significantly 30 minutes after coronary occlusion but improved to near preocclusion levels with post extrasystolic potentiation

mm Hg ($p < 0\,001$) Insignificant increases were noted in end diastolic left ventricular pressure from 5 6 ± 0 4 to 6 2 ± 0 8 mm Hg and segment length from 10 8 ± 1 2 to 11 1 ± 1 3 mm

The subsequent time course of responsiveness of the ischemic segment to PESP was observed over a period of three hours in nine dogs In seven of these dogs post occlusion pre extrasystolic shortening remained relatively stable while there was a progressive deterioration in PESP responsiveness (Figs 4 and 5) Thus, while PESP produced a 113 per cent mean increase in systolic shortening prior to occlusion, this response had decreased to only 5 per cent of resting shortening (p = N S) at three hours In the other two dogs this progressive loss of responsiveness was not observed In one animal occlusion produced a reduction in resting function to only 50 per cent of control in the second, a substantial spontaneous return of function followed occlusion and stabilized at a level more than twice that of the remainder of the group For this reason these two animals were treated separately

Discussion

This study demonstrates that atrial stimulation produces post extrasystolic potentiation of acutely ischemic myocardium even in the absence of resting shortening The degree of response to PESP was inversely related to the duration of ischemia Since no significant changes in left ventricular end diastolic pressure or segment length were observed the improvement in systolic shortening following PESP appears unrelated to changes in ventricular preload That the observed PESP responses occurred in part as a consequence of significant changes in left ventricular afterload is possible but doubtful aortic diastolic pressure decreased on the post extrasystolic beat due to the longer diastolic pause following the premature atrial stimulus, while systolic aortic pressure was augmented Because of these directionally opposite effects the total afterload could well have remained relatively unchanged Lastly since these pressure changes occurred for only a

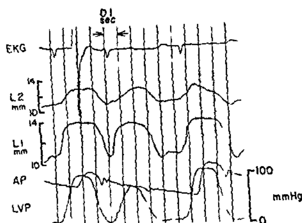


Fig 4 Loss of responsiveness to post extrasystolic potentiation The data illustrated are from the same animal depicted in *Fig 2* Two and one half hours after occlusion pre extrasystolic function is essentially unchanged and no shortening is seen on either length gauge (first beat) The central ischemic gauge (L) now fails to respond to the stimulus of PESP (third beat) while the adjacent gauge (L) continues to demonstrate improvement in systolic shortening

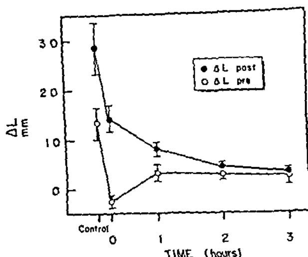


Fig 5 Time course of ischemic responsiveness to PESP Mean (± 1 SEM) systolic shortening (ΔL) of the ischemic zone is plotted against time after occlusion The open circles represent the pre extrasystolic beat (*ΔL pre*) and the solid circles and the post-extrasystolic beat (ΔL post) Following occlusion pre-extrasystolic shortening decreases and remains depressed for the duration of the study PESP produces a significant increase in systolic shortening for the first hour after occlusion but little change thereafter

single beat it is highly unlikely that regional function could have improved in response to augmented coronary flow especially in the face of total proximal occlusion The observed responses in epicardial segment function therefore probably reflect primary changes in contractile state induced by PESP[9, 3] rather than improved ventricular loading conditions or myocardial perfusion

The epicardium is much less sensitive to the effects of ischemia than is the endocardium The current data must be extrapolated to the intact heart only with caution therefore since the more profoundly ischemic deeper regions of myocardium may not respond in like fashion On the other hand a number of clinical ventriculographic studies have demonstrated PESP responsiveness of ischemic endocardium and pathologic studies reveal that such reversibly dysfunctional regions are histologically non infarcted[34] Therefore a substantial body of data suggests that the total loss of regional myocardial function secondary to ischemia need not be accompanied by muscle death and may in fact be completely reversible

The mechanism responsible for the variable function of ischemic myocardium remains unknown The *magnitude* of ischemia is not a simple determinant of ischemic dysfunction since not only can deeply ischemic myocardium retain contractile behavior[38] but also remote nonischemic muscle may become depressed[28] The *duration* of ischemia is also a complex determinant since reversible regional dysfunction probably persists for long periods of time in clinical ischemic heart disease[1, 5, 12, 1] In addition alterations of *ventricular loading* and *contractility* significantly influence ischemic segment function[23, 39] Although this study was not designed to investigate the mechanism of reversible dysfunction the observed time-dependency of PESP responsiveness emphasizes this complex interplay of factors

If cardiac stimulation is to be used in either experimental studies or in clinical cardiology to detect and quantify reversibly dysfunctional potentially viable myocardium PESP via atrial stimulation offers a number of substantial advantages in contrast to pharmacologic agents The stimulus is safely easily and rapidly delivered The dose is variable by alteration of coupling interval and is not limited by dose dependent side effects The magnitude of the response is large readily quantitated and highly reproducible The effects are transient and do not increase myocar

dial oxygen demand for more than 1 or 2 cardiac cycles Finally, major changes in preload, after load, and peripheral resistance do not persist following post extrasystolic potentiation[33] The variables affecting segmental performance are thus more narrowly controlled than is the case with peripheral vasodilators or inotropic agents For these reasons the method seems ideally suited for clinical use

Summary

The response of acutely ischemic myocardium to post extrasystolic potentiation (PESP) was evaluated in 11 mongrel dogs Mercury in silastic length gauges were sutured to the epicardial surface of the left ventricle left ventricular pressure was determined via an apical large bore catheter-transducer system and controlled by volume manipulation The anterior descending coronary artery was then ligated, and single premature atrial contractions were introduced via an external stimulator Thirty minutes after occlusion, shortening during ejection had decreased an average of 81 ± 8 per cent, from 1 30 ± 0 29 to 0 32 ± 0 05 mm PESP initially induced a marked restoration toward normal segmental contraction as systolic shortening increased significantly to 1 14 ± 0 23 mm Additionally paradoxic systolic expansion, when present, reverted to a normal pattern of contraction during PESP Responsiveness to PESP deteriorated progressively with time over 3 hours following occlusion until the muscle became essentially totally unresponsive to this stimulus It is concluded that a single premature atrial beat may be used to induce PESP and provides an effective stimulus for contractile reserve of acutely dysfunctional ischemic myocardium Loss of responsiveness to PESP may represent the progression to nonviability following acute ischemia

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Ventricular function and coronary hemodynamics after intravenous nitroglycerin in coronary artery disease

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A primary action of nitroglycerin is to relax vascular smooth muscle Accordingly, alterations in regional and systemic flow, venous pooling and changes in arteriolar and venous resistance may occur [1-4] Furthermore it has been suggested that nitroglycerin may also exert direct or indirect inotropic effects in isolated heart muscle preparations,[5, 6] as well as in the intact heart [7-9] The quantitative evaluation of both the vasodilator and contractile properties of sublingual nitroglycerin in man is impeded by the rapidly fluctuating unsteady state which is evoked because of the multiple sites of action and the secondary effects they produce [10] This study was designed to describe the effects on coronary subjects of intravenously infused nitroglycerin on left ventricular function and coronary blood flow, and on the systemic vascular pooling capacity

Material and methods

Studies were carried out in 14 coronary patients eight males and six females with a mean age of 48 8 years (range 29 to 62 years) (Table I) All patients gave informed consent for this study according to the declaration of Helsinki [11] Measurements were performed prior to the application of any contrast medium Left ventricular and aortic pressures were measured through catheters (pigtail, Cordis) which were directly connected to pressure transducers (Statham P23 Gb) The catheter system had a natural frequency above 20 Hz and a phase lag linear with frequency in this frequency range Overshoots as well as motion artifacts were not present at rest nor under the pharmacological studies All pressures were referred to zero level 10 cm above the table top Peak (dp/dt/P) was calculated by dividing the maximum rate of pressure development by its corresponding total isovolumic pressure Heart rate was kept constant at 10 to 15 per cent above individual spontaneous frequency by atrial pacing using a bipolar electrode and an external cardiac pacing device The pacing catheter was also used for the intravenous infusions A Goodale Lubin catheter (Ch 7) was inserted through the left cubital vein and introduced into the coronary sinus for coronary sinus blood sampling and for coronary blood flow determinations and a second venous catheter was placed into the pulmonary artery for continuous pressure measurement Since in our laboratory both the coronary sinus and pulmonary artery catheters are routinely introduced catheters in coronary patients, the external atrial pacing device was the only additionally introduced catheter in these patients Cardiac output was determined by thermodilution by the use of a modification of the method of Warner and Wood [12] Stroke work index, total peripheral resistance, and pulmonary vascular resistance were calculated by standard formulae [13]

Total coronary blood flow of the *left ventricle* (V) was determined by the argon inert gas method with gas chromatographic analysis of argon in arterial and coronary venous blood (Varian GmbH Darmstadt/GFR) Details of this method have been previously described [14, 17] Left ventricular oxygen consumption (MVO_2) has been calculated as the product of coronary blood

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flow (ml per min × 100 Gm) and the arterial-coronary venous oxygen difference (avdO) Arterial and coronary venous oxygen saturations have been measured by CO oximetry

Hemodynamic measurements were performed (1) under control conditions with two sets of control measurements taken at least 5 minutes apart (Table II) (2) under nitroglycerin infusion which was begun at 30 mcg./min and increased stepwise until systolic left ventricular or aortic pressure fell by an average of 20 per cent The infusion rate and maintenance dose necessary to continuously lower systolic left ventricular pressure by an average of 20 per cent was 62 mcg / min (range 40 to 92 mcg /min) The infusion was then continued and two sets of hemodynamic measurements were obtained at 5 minute intervals (Table II) (3) under the infusion of dextran parallel to the infusion of nitroglycerin Dextran (Macrodex Knoll A G /GFR) was intravenously administered utilizing a Harvard pump (series 921) and was increased stepwise until left ventricular systolic and end diastolic pressure had reached the initial values that is the control values before nitroglycerin At this level of restored pressure the infusion of both nitroglycerin and dextran was continued for 5 minutes to determine the hemodynamic parameters by two sets in 5 minute intervals The amount of dextran necessary for the re establishment of left ventricular pressure was then determined (mean 437 ml in 20 to 28 minutes)

Coronary blood flow measurements were performed three times (1) under control conditions (2) under nitroglycerin infusion (3) under both nitroglycerin and dextran infusion within the period of restored left ventricular pressure

Intravenous nitroglycerin was used as an aqueous dilution prepared from a specially produced 5 per cent sterile alcoholic nitroglycerin solution (Dynamit Nobel GmbH Koln /GFR) Statistical comparisons were made using Student s paired t test

Table I Patient population

Patient no	Age (yr)	Sex	ECG-diagnosis	Degree of stenosis MLCA	LAD	LCx	RCA
1	29	M	ST T wave changes	0	3	3	3
2	48	F	Ant sept infarct	0	4	2	4
3	52	F	Inf infarct	0	2	4	3
4	46	M	Inf infarct	0	4	4	3
5	62	M	Ant lat infarct	0	4	4	2
6	51	M	ST T wave changes	0	3	3	0
7	37	M	ST T wave changes	0	4	3	0
8	31	F	Ant lat infarct	2	4	2	4
9	61	F	Inf apical infarct	0	3	0	4
10	42	M	ST T wave changes	0	2	4	2
11	58	F	Ant lat infarct	2	4	4	0
12	56	M	Inf apical infarct	0	3	3	4
13	59	F	ST T wave changes	0	3	3	3
14	52	M	Inf infarct	0	2	3	4

Abbreviations MLCA = main left coronary artery LAD = left anterior descending coronary artery LCx = left circumflex coronary artery RCA = right coronary artery ant = anterior sept = septal inf = inferior lat = lateral.

Degree of stenosis by coronary arteriogram 0 = normal 1 = less than 50 per cent luminal narrowing = less than 5 per cent luminal narrowing 3 = 5 per cent luminal narrowing 4 = complete obstruction.

Results

Nitroglycerin infusion Under constant nitroglycerin infusion rate a 20 per cent decrease in systolic left ventricular pressure was associated with a 47 per cent decrease in left ventricular end diastolic pressure (Table III) Maximum rate of left ventricular pressure development (peak dp/dt) decreased by 13 per cent whereas peak (dp/dt/P) increased by 15 per cent At constant heart rate the cardiac index and stroke volume index decreased by 16 per cent As a consequence of the decreases of both stroke volume index and mean systolic pressure the stroke work index was reduced by 30 per cent (Table III) Total peripheral resistance index decreased by only 3 per cent whereas pulmonary vascular resistance index fell by 29 per cent Coronary blood flow of the left ventricle significantly decreased following intravenous nitroglycerin infusion by 13 per cent (mean) in comparison with the controls and MVO_2 decreased by 15 per cent (Table III)

Nitroglycerin plus dextran infusion The re establishment of left ventricular systolic pressure during nitroglycerin infusion by the parallel infusion of dextran was associated with complete normalization of left ventricular end diastolic pressure In contrast at comparable systolic and end-diastolic pressure and heart rate there were significant increases in peak dp/dt in pump parameters (stroke volume index cardiac index stroke work index) and in both coronary blood flow and MVO_2 (Table III Fig 2) The increases in these values ranged 10 to 28 per cent above controls

Table II Protocol for infusion of nitroglycerin and of both nitroglycerin and dextran

	Controls	NTG	NTG + dextran
Hemodynamics			
P_L	• •	• •	• •
P_{Ac}	• •	• •	• •
P_{Al}	• •	• •	• •
CO	• •	• •	• •
Coronary blood flow	•—•	•—•	•—•
Arterial O_2 saturation	• •	• •	• •
Cor venous O_2 saturation	• •	• •	• •
Hemoglobin	•	•	•
Hematocrit	•	•	•
Nitroglycerin infusion	from 0 to 60 min		
Dextran infusion	from 25 to 60 min		
Time [min]	10 5 0	5 10 15 20	25 30 35 40 45 50 55 60

Vascular pooling capacity of nitroglycerin The volume expansion necessary for the complete re establishment of left ventricular pressures averaged 437 ml (Table III)

Discussion

This study suggests that the hemodynamic effects of nitroglycerin in coronary artery disease are characterized by a moderate positive inotropic effect on the myocardium as well as by a diastolic and systolic unloading of the heart After compensating for changes in heart rate as well as for nitroglycerin induced changes in left ventricular end diastolic pressure and afterload significant increases in left ventricular pump parameters, contractility indices as well as coronary blood flow and MVO_2 were demonstrated Thus by experimentally reversing some of the hemodynamic responses to nitroglycerin through control of heart rate left ventricular end diastolic pressure, and afterload a direct effect of nitroglycerin on left ventricular performance and coronary blood flow was elicited Finally, the vascular pooling effect of nitroglycerin has been quantitatively evaluated by the direct measurement of volume expansion necessary for the re establishment of both left ventricular and pulmonary artery pressure during continous nitroglycerin infusion

Nitroglycerin infusion Systolic unloading was associated with a 3 per cent decrease in total peripheral resistance index This may be attributed to the decreases in cardiac index (16 per cent) parallel to pressure change so that the calculated peripheral resistance index did not change significantly In contrast pulmonary vascular resistance index fell by 29 per cent This difference indicates that the effect of intravenously administered nitroglycerin on pulmonary vascular resistance was far more pronounced than on the peripheral arterial vascular bed

The decrease in stroke volume during nitroglycerin infusion at a fixed heart rate may be attributed primarily to a reduction in preload This is indicated by the considerable decrease in left ventricular end diastolic pressure (–43 per cent) in these patients (Fig 1) Since spontaneous heart rate did not exceed the pacing rate obtained by the pacing device and basic heart rates at the end of the study (under the nitroglycerin plus dextran state) were essentially normal when compared with the control state, any baroreceptor mediated increases in heart rates can be excluded

The decreases in coronary flow and in MVO_2 during nitroglycerin may be related to the reductions of some of the major determinants of myocardial energy demand[8, 18, 20] Wall tension which results as a consequence of ventricular pressure volume and wall thickness presumably was reduced because of the decrease in end diastolic (43 per cent) and systolic pressure (20 per cent) and in end diastolic volume[19] The external cardiac work was considerably reduced as evidenced by the decrease in left ventricular stroke work index (30 per cent) Thus two of the determinants of myocardial energy demand (tension cardiac work) were lowered and may be appropriate to explain the decrease in MVO_2 On the other hand left ventricular contractility was moderately enhanced under the influence of nitroglycerin (see below) and an increase in

contractility has been found associated with an increase in MVO_2[8, 20] However it may be reasonable to assume that the reductions in wall tension and in stroke work quantitatively override the increase in contractility as related to the ventricular energy demand so that a net decrease in the overall oxygen consumption occurred

Nitroglycerin plus dextran infusion Re-establishment of left ventricular pressures through volume expansion (mean 437 ml) by dextran conceivably could influence ventricular and systemic hemodynamics as a specific result of dextran The hematocrit was decreased non significantly by 2 per cent (mean) which does not affect hemodynamics [1, 5] Likewise primary effects of dextran on blood viscosity as well as changes in vascular reactivity in erythrocyte characteristics and in cellular aggregation which may alter blood viscosity can be largely excluded since a 2 per cent reduction from normal hematocrit reduces blood viscosity (shear rate 20/sec) by approximately 1 to 3 centipoise[2] that is by 2 to 6 per cent These small viscosity changes induced by dextran seem to have no effect on contractile function and hemodynamics in situ [5] On the other hand infusion of dextran in coronary patients may exert an increase in left ventricular pressures with or without changes in stroke volume [2] However these changes occurred when starting from control conditions whereas in this study dextran was exclusively used to restore left ventricular pressures to the initial values Accordingly it seems unlikely that pressure changes may have contributed to the changes in left ventricular function and coronary hemodynamics Moreover utilizing comparable infusion rates of dextran as in this study Khaja and colleagues found no alterations in left ventricular contractility indices in coronary patients at fixed heart rate and stroke volume index increased only if the left ventricular end diastolic pressure was raised However in none of the 14 patients of this study did left ventricular end diastolic pressure under the infusion of both nitroglycerin and dextran exceed the control values before nitroglycerin Thus the procedure of restoring the nitroglycerin induced pressure decrease by dextran infusion (under atrial pacing) seems appropriate to examine the effects of nitroglycerin on ventricular performance independent of parallel changes in systolic and end-diastolic pressures and on heart rate

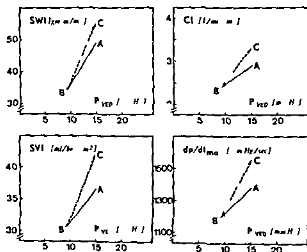


Fig 1 Relationships between left ventricular end-diastolic pressure and hemodynamic measures *The base and peak of the arrows* indicates mean values from all patients A = controls B = nitroglycerin infusion C = nitroglycerin plus dextran infusion

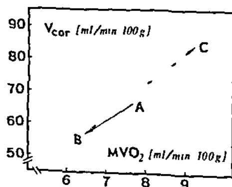


Fig 2 Left ventricular oxygen consumption (MVO_2) and coronary blood flow (V_{cor}) *The base and peak of the arrows* indicates mean values from all patients A = controls B = nitroglycerin infusion C = nitroglycerin plus dextran infusion

The combined nitroglycerin plus dextran infusion indicates that nitroglycerin itself moderately increases myocardial contractility The rise in stroke volume index (14 per cent) and in cardiac index (13 per cent) occurred at constant end diastolic pressure afterload and heart rate when compared with the initial values Secondly the rate of left ventricular pressure development as indicated by the rise in peak dp/dt (12 per cent) was increased Thirdly peak (dp/dt/P) which under the influence of nitroglycerin alone possibly may have been overestimated because of the marked fall in left ventricular end diastolic pressure[2] was significantly enhanced under nitro

Table III Hemodynamic findings in 14 patients receiving intravenous nitroglycerin as well as intravenous nitroglycerin and dextran

Patient no		P_L [mm Hg]	P_{LVEDP} [mm Hg]	Peak dp/dt [mm Hg/sec]	Peak (dp/dt/P) [1/sec]	CI [L/min m²]	SVI [mL/beat m²]
1	C	110	10	1400	24	2 52	3[illegible] 0
	NTG	85	5	1250	27	2 21	30 0
	NTG + D	115	10	1600	28	3 47	4[illegible] 5
2		138	8	2300	28	3 36	34 4
		92	5	1650	32	2 51	25 [illegible]
		135	8	2900	32	3 59	37.2
3		105	20	1000	19	3 18	38 9
		98	12	950	25	2 4	29
		112	20	1250	26	3 42	41 [illegible]
4		108	9	1350	18	2.38	33.9
		89	5	1100	22	1 92	28 9
		108	9	1750	24	3 42	4[illegible]
5		118	12	950	17	2 76	39 1
		85	8	750	20	2 39	33 [illegible]
		116	12	1000	21	3 02	42.4
6		132	20	1750	29	3 64	48 9
		105	10	1900	33	3 48	47.3
		120	20	1900	33	3 45	46 8
7		130	16	1100	19	2 73	33 0
		110	12	1000	18	1 88	[illegible]
		112	16	1100	20	2 73	33 0

Abbreviations C = control NTG = nitroglycerin infusion D = dextran infusion P_L = peak systolic left ventricular pressure P = left ventricular end diastolic pressure peak dp/dt = maximum rate of left ventricular pressure development peak (dp/dt/P) = ratio between the maximum rate of left ventricular pressure development and its isovolumic total pressure CI = cardiac index SVI = stroke volume index SWI = stroke work index TPRI = total peripheral resistance index PVRI = pulmonary vascular resistance index V = coronary blood flow of the left ventricle MVO = oxygen consumption of the left ventricle
SD = standard deviation P values represent the difference between C and NTG infusion or between C and both NTG and D infusion as calculated by the paired Student s t test NS = not significant % Δ average per cent change between C and NTG or between C and (NTG plus D)

glycerin at normal left ventricular end diastolic and systolic pressure (18 per cent) Thus, the changes in isovolumic contractility indices (peak dp/dt, peak [dp/dt/P]) indicate increased isovolumic contraction velocity,[27] whereas the changes in stroke volume index indicate increased auxotonic performance There are theoretical objections to determination of dp/dt and peak (dp/dt/P) with an external transducer (pigtail catheter and Statham transducer) However direct in vivo comparison with a catheter tip manometer at heart rates of 75 to 150/minute has shown that the two methods correspond closely to a value of 2 000 mm Hg/sec [24] Except for patient No 2 this value has not been reached in this study

It may be of interest that other clinical studies also suggest an inotropic action of nitroglycerin as evidenced by alterations in ejection fraction wall motion, velocity of circumferential fiber shortening, or rate of left ventricular pressure development [7,9,8,31] However, evaluation of contractility in situ may be difficult because of the simultaneous alterations of hemodynamic variables after sublingual nitroglycerin [2] On the other hand, a possible increase in ventricular compliance could increase diastolic volume at a given diastolic pressure This could lead to an increased wall tension at a given afterload and end diastolic pressure which in turn could be responsible for the observed increases in contractility However a change in compliance has not yet been established in man under the influence of nitroglycerin, and there are no alterations in the length-tension relationships of isolated cat and human ventricular myocardium [5,6,31,33] The assumption of a direct positive inotropic effect of nitroglycerin is substantiated by studies in animal experiments and in the isolated human atrial and ventricular myocardium in which increases of the extent of shortening of the

SWI [gm m/m]	HR [beats/min]	TPRI [mm Hg/min/L m]	PVRI [mm Hg/min/L m]	V [ml/min 100 g]	MVO [ml/min 100 g]	Volume infused [ml]
45 2		34 9	6 6	76	9 0	
30 6	73	30 1	5 2	72	8 0	500
64 6		26 0	4 7	112	11 8	
58 5		31 5	5 1	60	7 5	
28 6	97	26 9	5 6	50	5 9	200
61 7		29 1	4 7	110	11 4	
4? 3		27 3	4 1	63	7 4	
32 7	8?	34 0	2.1	59	6 6	150
49 4		26 4	3 8	72	7 8	
43 3		34 5	5 9	55	5 6	
31 0	70	35 4	6 2	44	4 4	400
60 4		24 0	4 1	45	8 8	
53 7		32 9	6 5	–	–	
33 0	71	27 8	5 9	–	–	375
57 1		28 3	6 0	–	–	
71 2		28 1	6 3	73	8 1	
57 9	74	23 5	3 7	71	8 9	575
60 5		27 0	6 7	89	8 2	
48 9		38 5	6.2	59	8 8	
28 7	83	47 0	5 3	50	5 7	
40 8		33 8	6 2	60	9 1	500

velocities of isotonic concentration and relaxation and of the rate of isometric tension development in afterloaded and in isometric studies have been demonstrated[8] The increases in these parameters which were found at constant preload afterload and frequency of stimulation varied 12 to 27 per cent in comparison with the controls Moreover equivalent shifts of the force-velocity relationships of both concentration and relaxation to higher values of velocity and tension occurred at constant preload

The increase in total coronary blood flow (28 per cent) may be the consequence of direct coronary dilation or an increased myocardial energy demand Since arterial-coronary venous oxygen difference was nearly unchanged it seems unlikely that the total coronary blood flow increased primarily due to coronary dilation The increase in MVO indicates increased metabolic activity which is evidenced by the almost equal increases in both coronary blood flow (V) and myocardial oxygen consumption (MVO) (Fig 2) Under nitroglycerin plus dextran both tension development and heart rate may be neglected as to their influence on the over all oxygen consumption since they were controlled (heart rate) or presumably normalized (tension) Accordingly contractility and fiber shortening increased significantly and may contribute to the increased energy demand under the influence of nitroglycerin at stabilized pressures In this regard the assumption of oxygen wasting[15] may be unnecessary since the coronary and metabolic effects occurred in quantitative accordance with changes of mechanical or contractile function of the left ventricle[8, 9]

Vascular pooling capacity The systemic vascular pooling capacity of nitroglycerin has been quantitatively determined during restoration of left ventricular end diastolic and systolic pressure by the infusion of dextran parallel to nitroglycerin infusion The internal phlebotomy induced by nitroglycerin averaged 437 ± 128 ml at an infusion rate of 62 mcg /minute (mean) This vascular pooling probably is due to venodilation[3] The vascular pooling capacity provides an explanation for the fall in cardiac output and in derived measures (cardiac index stroke volume index) as well as for the decreases in left ventricular systolic end diastolic and in pulmonary

Table III continued

Patient no	P_{LV} [*mm Hg*]	P_{LVEI} [*mm Hg*]	*Peak dp/dt* [*mm Hg/sec*]	*Peak (dp/dt/P)* [*1/sec*]	*CI* [*L/min m*]	*SVI* [*mL/beat m*]
	108	16	900	23	3 11	4[illegible]0
8	90	9	780	26	3 03	41 0
	104	17	900	27	3 39	46.0
	98	17	1300	26	2 54	28 2
9	83	10	1200	30	1 75	19 5
	100	16	1400	29	3 21	35 9
	120	18	1650	22	2 6	36 1
10	90	10	1100	28	2 14	[illegible]
	120	18	1900	28	2 64	37 1
	112	12	1500	21	3 34	34 5
11	90	8	1280	23	3 03	3[illegible] 5
	117	13	1600	22	3 74	44 [illegible]
	120	12	1520	22	3 08	30 3
12	106	8	1320	25	2 97	[illegible]6 1
	120	12	1520	27	3 97	39 8
	130	20	1300	24	2 71	38 8
13	108	9	1400	26	2 4	33 9
	128	20	1500	27	2 71	38 8
	120	17	1300	22	2 56	36 0
14	90	7	1100	27	1 99	[illegible]8 0
	105	16	1400	28	3 16	44 5
Mean ± SE (Control)	118 ±12	15 ±4	1380 ±368	22 4 ±3 6	2 89 ±0 39	36 4 ±5 1
Mean ± SE (NTG)	94 ±9	8 ±2	1199 ±312	25 9 ±4 2	2 44 ±0 52	30 6 ±7 1
P value	<0 001	<0 001	<0 01	<0 001	<0 001	<0 001
% Δ	−20%	−43%	−13%	+15%	−16%	−15%
Mean ± SE (NTG + D)	115 ±9	15 ±4	1551 ±494	26 6 ±3 8	3 28 ±0 39	41 5 ±4 [illegible]
P value	NS	NS	<0 005	<0 001	<0 005	<0 005
% Δ	−2%	±0%	+12%	+18%	+13%	+14%

artery pressures Similarly, this effect may also account for diminution of ventricular size observed in man[19] and may help to explain the beneficial action of nitroglycerin in some patients with acute left ventricular failure and pulmonary edema[3, 40] In these conditions marked elevations of left ventricular end diastolic and/or pulmonary artery wedge pressure may occur which can be considerably reduced by phlebotomy or by nitroglycerin On the other hand it is possible that depletion of intravascular volume in coronary patients with normal or only moderately elevated left ventricular end diastolic pressure may cause a low cardiac output and decreased coronary arterial perfusion pressure and hence worsening of myocardial ischemia[40, 41] Therefore the indication of intravenous nitroglycerin in patients with coronary artery disease should be determined primarily on the basis of the systemic blood pressure and left ventricular end diastolic pressures

Summary

Left ventricular dynamics as well as systemic and coronary hemodynamics were determined in 14 patients with coronary artery disease (1) under control conditions (2) under intravenous infusion of nitroglycerin, (3) under continued infusion of nitroglycerin with restored arterial and pulmonary artery pressures induced by the parallel infusion of dextran Heart rate was kept constant by atrial pacing

SWI [gm m/m]	HR [beats/min]	TPRI [mm Hg/min/L m]	PVRI [mm Hg/min/L m]	V [ml/min 100 g]	MVO [ml/min 100 g]	Volume infused [ml]
49 7		29 3	4 5	65	7 9	
4[illegible] 4	74	25 7	2.3	57	6 8	
51 3		2[illegible] 8	4 1	65	8.2	500
29 [illegible]		31 8	6 3	56	5 6	
18 0	90	39 1	5 1	54	5 9	
38 6		[illegible]4 3	5 0	63	6 7	500
47 7		38 0	5 4	64	8 8	
30 3	72	3[illegible] 9	[illegible] 8	47	6 3	
49 0		37 4	5 3	69	8 9	550
44 6		26 6	6 0	87	8 3	
34 0	93	24 3	5 3	65	6 4	
59 5		24 4	5 3	94	10 7	530
4[illegible] 5		31 8	5 2	68	7 4	
33 0	10[illegible]	29 1	4 0	59	6 7	
[illegible]4 4		[illegible]4 7	4 0	9[illegible]	10 5	540
[illegible]5 4		38 7	5.5	—	—	
43 4	0	36 4	1 7	—	—	
54 3		37 9	5 5	—	—	400
48 0		38 0	5 0	—	—	
[illegible]9 7	71	34 6	1 5	—	—	
50 8		26 3	4 1	—	—	400
48.6	80	33 0	5 6	66	7 7	
±9 6	±11	±4 2	±0 8	±9 6	±1 2	
33 8	80	31 9	4 0	57	6.5	
±9 [illegible]		±6 5	±1 6	±9 3	±1 2	
<0 001		NS	<0 001	<0 001	<0 01	
−30%		−3%	−29%	−13%	−15%	
53 7	80	[illegible]8 [illegible]	5 0	85	9 3	
± [illegible] 7		±4 7	±0 9	±2[illegible]	±1 6	437 ±128
NS		<0 001	<0 005	<0 01	<0 005	
+10%		−14%	−1[illegible]%	+[illegible]8%	+21%	

Intravenous nitroglycerin infusion resulted in a significant reduction in left ventricular systolic (20 per cent) and end diastolic pressure (43 per cent) peak dp/dt (13 per cent) cardiac index (16 per cent) stroke volume index (15 per cent) and stroke work index (30 per cent) Peak (dp/dt/total pressure) increased (15 per cent) Pulmonary vascular resistance markedly decreased (29 per cent) whereas total peripheral resistance did not change significantly (−3 per cent) Both coronary blood flow of the left ventricle (13 per cent) and myocardial oxygen consumption (15 per cent) decreased parallel to the reduction in preload and afterload The action of nitroglycerin at restored left ventricular and pulmonary artery pressures was characterized by increase in peak dp/dt (12 per cent) peak (dp/dt total pressure) (18 per cent) cardiac index (13 per cent) stroke volume index (14 per cent) and stroke work index (10 per cent) Both coronary blood flow (28 per cent) and myocardial oxygen consumption (21 per cent) increased parallel to the enhancement of ventricular performance

The results demonstrate that intravenous nitroglycerin produces effective diastolic and systolic unloading of the heart associated with reduction in myocardial oxygen consumption and in coronary blood flow There was marked vascular pooling which quantitatively averaged 437 ± 128 ml This occurred concomitant with a 43 per cent decrease in left ventricular end diastolic pressure or a 20 per cent decrease in peak

systolic pressure Significant coronary dilating properties of nitroglycerin could not be detected in these coronary patients The increase in left ventricular contractility indices at restored pressure suggests a moderate but significant positive inotropic effect of nitroglycerin

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The difference vector Assessment of effects of changes or interventions

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In studying the electrocardiographic changes after any procedure or disease, one usually looks at alterations in waveform amplitude duration, or vector direction We wish to discuss another approach, i e , the vector which represents the difference between the postoperative and pre operative vectors The vectorcardiogram (VCG) is the resultant of all the forces occurring during the electrical activity of the heart At a given instant of time large areas may be excited simul taneously If the change affects only a portion of the heart there may be normal spread over parts of the heart as well as spread through the injured portion resulting in an abnormal resultant vector

Bayley[1] referred to the dead zone vector which summates with the normal vector in cases of infarction He pointed out that this vector exists only during progress of accession over regions of the myocardium containing the dead tissue If one assumes that excitation is normal in unaffected tissue then the difference between post infarction and pre infarction vectors should be due entirely to the abnormal excitation This approach has been used by Flowers and colleagues[2,3] in constructing difference surface potential maps

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Digression on vectors

Although the properties of vectors are discussed in standard textbooks we wish to point out a few aspects of the difference vector as an aid in understanding the results In Fig 1A the vector difference between vectors T and U is a vector U-T drawn between the tips of T and U Without loss of generality vector U-T can be transferred to the origin

In Fig 1B vector T has increased to vector U without change in direction Vector U-T lies along the same axis If T decreased in magnitude U-T would lie along the same axis but point in the opposite direction (Fig 1C) Fig 1D shows that the difference vector U-T can be larger than either vectors T or U The magnitude (as well as the direction) of the difference between two vectors depends, therefore both on the magni tudes of the original vectors and the angle between them

Methods

Infarcts or ischemic areas were produced in young pigs (6 to 12 weeks old) by ligating the left anterior descending coronary artery (LADA) or one of its branches VCGs were obtained before and one to two weeks after surgery using the lead system previously described[4] Upon termination, the heart was excised sectioned, and weighed The location and extent of the infarcts were determined at this time

Vector spatial magnitudes and directions were found by applying X Y and Z signals to an analog computer The difference vectors were calculated for the postoperative and preoperative peaks of the spatial magnitude (M) curves

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Curves of M M, and M were plotted for preoperative and postoperative cases At each instant of time we computed

$$M_D = M_2 - M_1$$
$$M_{yD} = M_2 - M_{y1}$$
$$M_D = M_2 - M_1$$

Here M_D is the difference between postoperative and preoperative values of M at a given instant of time etc M_t is then the X component of the difference vector M_t M_D H_D and $V°_t$ are found as before and are given by

$$M_t = \sqrt{M_D + M_{yD} + M_D}$$

$$H_D = \tan^{-1}\left(\frac{M_t}{M_D}\right)$$

$$V°_D = \sin^{-1}\left(\frac{M_{yD}}{M_D}\right)$$

Results

The M curves had one to three peaks[5] These peaks were designated M_1 M and M_3 and corresponded to excitation of septum ventricular free walls and basal portions of ventricles and septum Since the experimental animal was the young growing pig and since dipole moment depends on heart size difference vectors were computed for a normal pig over a two week period (Fig 2) It is seen that there was little change in vector direction during this time

In another animal (pig No 13) the LADA was ligated high up above the branches The heart fibrillated but was brought back by electric shock treatment There was a large infarct in the wall of the left ventricle extending nearly to the apex The infarcted area was 1 6 by 2 0 cm and was 3 5 mm thick The LV wall thickness was 7 4 mm Fig 3 shows preoperative postoperative and difference vectors for the M M and M peaks The small M control vector pointed to right anterior (ventrad) and up (cephalad) One week after the ligation M shifted to the right but still upwards The M difference vector D pointed to right posterior and up (Fig 3) The LADA supplies the anterior wall and septum including about one third of the RV and anterior and lateral portion of the LV free wall and apex The position of the D vector could be due to an infarcted region of the anterior portion of the septum causing the vector to point towards the right posterior rather than anteriorly

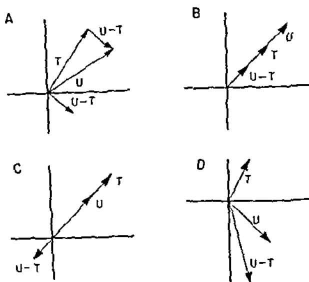


Fig 1 Diagrams showing two vectors T and U and the difference vector U-T (see text for explanation)

The M_2 vector pointed initially to left posterior and down The seven day postoperative vector shifted in a counterclockwise (ccw) direction so that it pointed nearly directly posteriorly and down The difference vector D however pointed to the right slightly posterior and up This is consistent with the presence of an infarct on the anterior wall of the heart

The M_3 vector initially directed towards the left posterior and upwards also shifted ccw The difference vector D_3 was close to D in position Vectors D, D and D_3 should represent the effect of the infarction better than the postoperative vectors alone

Pig No 35 had no M_2 peak but changes in the M_1 and M_3 peaks were very similar to those for pig No 13 In pig No 35 the LADA was ligated about one third of the way down from the base just above the apical branch There were ischemic zones on the septum facing the left ventricle (1 5 × 1 × 0 2 cm) on the apical endocardium (0 25 cm thick) and on the LV middle endocardium (3 × 2 × 0 15 cm) With this extensive involvement it is not surprising that both M_1 and M vectors were altered

In pig No 51 (Fig 4) a region of the right ventricle (RV) was also infarcted The M_1 vector initially to the right anterior and horizontal shifted after infarction to left anterior and upwards (Fig 4) The difference vector D was also in this direction In this animal the tie was located half way between base and apex on the

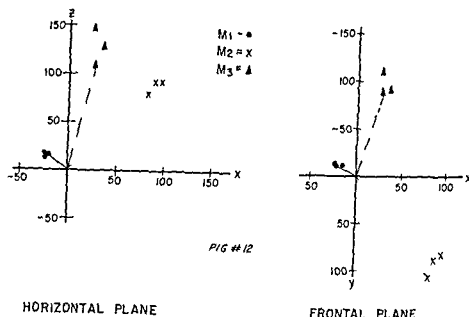


Fig 2 Effects of two weeks growth on horizontal and frontal plane vectors of a normal pig Initial age was six weeks Lines are drawn for the initial vectors only Difference vectors were very small and are not shown In all diagrams +X is to left +Y down (caudad) and +Z posterior

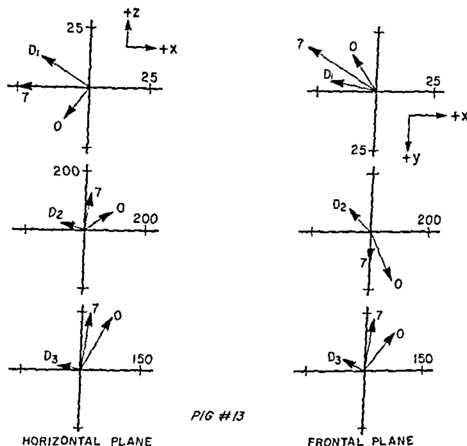


Fig 3 M M₂ and M peak vectors for pig No 13 with transmural infarct on wall of left ventricle Vectors are preoperative (zero days) postoperative (7 days) and the difference vectors (D) Note differences in scales

LADA Infarction was found on the RV (3 5 × 0 25 × 0 25 cm) the septum (3 × 1 5 × 0 4 cm) the apex (2 8 × 1 2 × 0 5 cm) and the LV free wall (2 3 × 2 3 × 0 3 cm) Changes in the M_3 vector (Fig 4) were similar to those for pig No 13 (Fig 3) except that D_3 was to the right anterior and slightly down instead of to the right posterior and somewhat up The fact that D_1 pointed to the left away from the RV may have been caused by the RV involvement

Fig 5 shows M control post ligation and difference vectors for two pigs which had infarcts

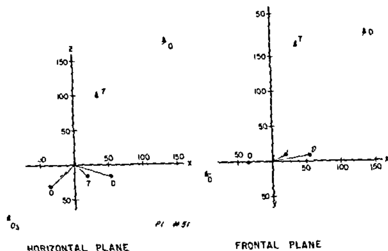


Fig 4 M and M peak vectors for pig No 51 There was an infarct on the right ventricle as well as on the septum apex and LV The initial difference vector D points towards the left away from the infarcted right ventricle

extending into the septum apex and LV anterior free wall Pig No 32 had the largest infarct involving 3 85 Gm of the LV free wall The control vector pointed to the right anterior and down Eight days after the ligation the vector had shifted to left posterior and down with the difference vector left posterior and up Pig No 33 had an infarct in the same general location but the septum was somewhat more involved than the LV free wall or apex The zero and seven day vectors pointed to left posterior and down but the difference vector was left posterior and up Even though the control vectors for the two pigs had quite different directions the difference vectors were in the same spatial octant M occurs at about the time of the rapid shift of the normal vector from anterior to posterior so that control vectors can be either anterior or posterior For 17 control pigs the mean H vector was –5 degrees but with a standard deviation of 76 degrees The normal V° angle for these controls was 50 degrees with S D = ± 19 degrees

In pig No 23 ligation of the left circumflex coronary artery produced a small (1 75 Gm) infarct in the base of the LV The control M_1 vector pointed to left posterior and up Seven days after the ligation the vector shifted to nearly directly posterior and up The difference vector however was to the right and upwards

Because most of the pigs did not have all three M M and M peaks we also examined the difference vector during the entire QRS complex Fig 6 shows curves of M H and V° during QRS for pig No 51 which is the same animal as in Fig 4 Fig 6A shows that the normal M curve had two peaks M_1 and M Seven days after ligation of the LADA the curve had changed significantly The M_1 peak was no longer evident The dipole moment increased between 15 and 40 per cent of QRS duration (PQD) and an M_2 peak appeared From 40 to 80 PQD M decreased M_2 dropped by nearly one third Since this pig had infarcted areas in RV septum LV and apex there were changes throughout most of QRS

Fig 6A also shows the difference vector magnitude curve This is not generally equal to the algebraic differences between the other two curves It is seen that M_D has peaks at about 25 and 55 PQD The peak at 25 PQD is due to the infarcts in RV and septum The later peak would correspond to infarct in the apex and LV

Fig 6B shows curves of the horizontal angle H° during QRS The preoperative H° curve is normal i e the horizontal plane vector swings from right anterior to left anterior and then left posterior The post ligation curve is somewhat similar except that the swing from anterior to posterior is more gradual The difference H° curve however shows that the horizontal difference vector pointed to the left posterior until 35 PQD and then swung rapidly to the right anterior It then stayed in the right anterior but with a movement towards left anterior at about 70 PQD Up to 35 PQD M_1 pointed away from the RV and septum The later anterior direction was caused by the infarcts in the LV and apex and possibly also a change in the excitation pathway

Fig 6C shows the variation of the vertical

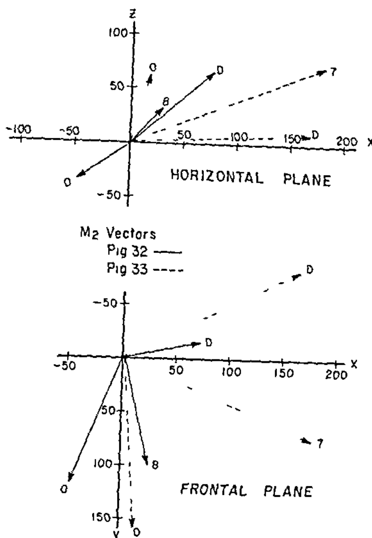


Fig 5 M peak vectors for pigs No 32 (solid lines) and pig No 33 (broken lines) Although the control vectors were nearly oppositely directed in the horizontal plane the difference vectors had a similar orientation

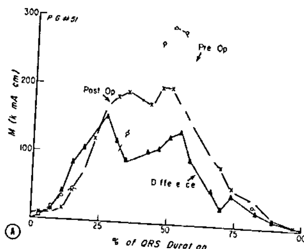
angle, V° The preoperative curve was again normal showing an initial superior direction followed by inferior between 18 and 43 PQD After this time the direction was superior again The postoperative V° curve was similar in shape but was displaced in a superior direction The maximum downward angle with the horizontal plane was 35 degrees instead of 85 degrees The V° curve of the difference vector did not resemble either the normal or postoperative curve but had two positive (downward) peaks and two negative (upward) peaks The first peak of M_D at 27 PQD pointed to the left horizontal and somewhat posterior The second peak at 54 PQD corresponding fairly closely with M_1 pointed to right anterior and downwards nearly opposite to the normal M_1 direction

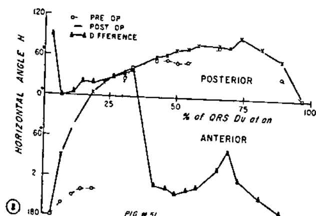
Another example of the usefulness of the difference vector is shown in Fig 7 The data were taken from Table III of a previous publication on the changes in spatial dipole moment after surgical repair of atrial septal defect It was found that the M peak, corresponding to excitation of ventricular free walls increased after the shunt was repaired The explanation was offered that the RV vector was increased by the larger blood volume in this ventricle This opposed the LV vector, resulting in a smaller resultant vector A problem was that after surgery, with the diminution of the RV vector, one would expect the magnitude to increase but with a leftward shift of the resultant vector, instead of the rightward shift which was found Fig 7 shows a possible explanation of this apparent inconsistency The reason lies in the direction of the difference vector which represents the effect of the increased blood in the right ventricle This vector points to right posterior instead of right anterior as one might assume If the difference vector had pointed to the right anterior, there would have been a leftward shift of the postoperative vector In the case of secundum atrial septal defect, the postoperative vector may be considered more nearly normal than the preoperative vector because normal blood volumes are restored Thus we believe the original explanation[7] was correct and the rightward shift was due to the abnormal RV vector

Discussion

Vectorcardiographic diagnosis of infarction is based on the concept that the dead tissue contributes no voltage to the resultant vector which consequently tends to point away from the site of the infarction If the infarct is small or involves only a limited portion of the myocardium, the dead zone vector summates with the vector due to excitation of normal myocardium and only partially points away from the inactive tissue

In Fig 4 the M_1 vector shifted from right anterior to left anterior seven days after ligation of the LADA The difference vector points somewhat more to the left but in this case the seven day vector is fairly close to the difference vector The M_1 difference vector is pointed in an entirely different direction from the M_1 seven day vector, however The M_3 seven day vector is shifted towards left posterior and upwards so that a diagnosis of an inferior location of the infarct





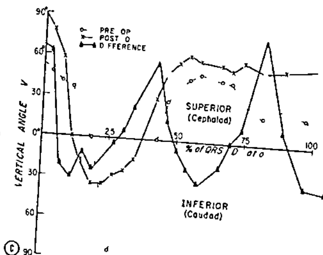


Fig 6 Curves of M H and V during QRS for pig No 51 The curves show control values, seven days after ligation of the LADA and differences vectors

might be made The D vector points towards right anterior and down more in keeping with the actual location of the injured tissue

We have studied primarily the effects of infarcts on the three spatial magnitude dipole moment peaks These peaks are however representative of the heart s excitation since they occur during excitation of septum and right ventricle free walls of both ventricles and late basal excitation of LV and septum The location and extent of the infarction determines which peaks are affected An infarct in RV alone would involve M and M peaks whereas a transmural infarct in the LV might affect both M_1 and M peaks

Whether or not excitation is normal in uninjured areas of the heart would depend on indirect effects of the infarct such as altered hemodynamics contractility etc Up to the time the excitation wave reaches the affected region the spread should be normal After reaching the infarcted tissue however it is possible that new wavefronts might be established or the time sequence of excitation might be altered so that an abnormal terminal pattern might result Intra infarction excitation waves may follow circuitous routes resulting in large time differences in local excitation Therefore late ECG patterns may be abnormal even though the infarct involved regions of the heart energized earlier

A complicating factor is that the pig heart excitation is different from other species such as the human being dog or monkey [9] Hamlin and associates studied excitation of the minipig heart which has a QRS duration of about 80 msec The young pigs used in our study had a mean QRS

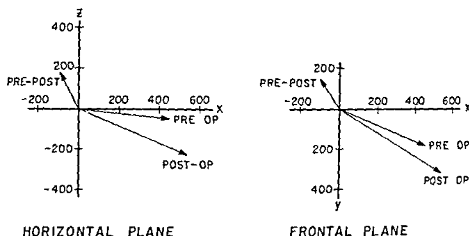


Fig 7 Change in vectors after surgical correction of secundum atrial septal defect Data are from Reference No 7 The difference vector represents the effect of the increased volume of blood in the right ventricle

duration of 40 5 msec We have assumed that the excitation is similar to that for the adult minipig heart and have expressed times as percentage of QRS duration in order to compare results

There are four stages in the pig heart excitation [9] From zero to 13 to 19 PQD the apical third of septum is excited from left to right and also from right to left There would probably also be some spread along the axis of the septum This would result in three vectors, the largest directed towards right anterior and upwards, a smaller oppositely directed vector and a third small vector towards left/right posterior and upwards An infarct in the left ventricular side of the septum would eliminate or reduce the left to right forces so that the smaller right to left forces would predominate, producing a vector to the left posterior This might explain the early changes shown in Fig 6

The next stage consists of excitation of RV in a direction downwards to the left anterior and a smaller LV wave front in the opposite direction There is also excitation of the septum in an apex to base direction The larger RV force is opposed by the LV and septal forces so that the net voltage is not too large This stage is from about 15 to 40 PQD An RV infarct would reduce the RV force so that the net vector would instead be pointed upwards to left and posterior In Fig 6 at 25 PQD the normal vector pointed to the right anterior and downwards The difference vector at this time is directed towards the left posterior and only slightly downwards The postoperative vector increased because of less cancellation and the difference vector magnitude was large

The third stage (40 to 75 PQD) consisted of rapid spread through the remaining ventricular walls and continued apex to base septal excitation [9] The normal vector is pointed up posterior and either left or right (Fig 6) Basal portions of both ventricles are excited at this time During the final stage activation of the basal septum is completed Fig 6 shows that the difference vectors from 40 to 75 PQD were nearly opposite the normal vectors as they were directed toward right anterior and down This might be caused by an infarct in the septum or on the caudal portion of the anterior wall which is activated rather late [9] The earlier abnormal spread might in part cause the abnormal activation at this time

The position of the pig heart within the thorax is similar to the heart s position in the dog [10] The RV lies above and to the right of the septum The septum makes an angle of about 30 degrees with the vertical axis (head-foot) and 45 degrees with the transverse plane [10] The heart tilts forward from dorsad to ventrad with the apex near the anterior wall

One would expect that with the tangential and oppositely directed excitation of the ventricles the VCG would be quite different from that of the dog or human being All of our controls however showed H° and V° curves during QRS which closely resembled such curves for dogs and human beings The main difference was that the M_3 vector was largest in the pig whereas in the dog and human being M was the largest peak

The lowered M vector in the pig might be due to the effects of intracardiac blood which enhanced voltages due to radial spread and attenuated voltages due to tangential spread [11, 12] This does not explain why the H° and V° curves are so similar in all three species however

Summary

Vector dipole moments were measured on young pigs before and one week after ligation of the left anterior descending coronary artery Vectors were obtained for the three peaks of vector spatial magnitude M Preoperative post operative and difference vectors were measured for each peak If excitation is normal except through the infarcted tissue the difference vector should be more closely related to the infarct because the normal excitation cancels out It was found that the postoperative vector was changed by the infarct but that the difference vector was a better indication of infarction This paper was designed to introduce the method using experi mental data for a small number of pigs

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Effects of proximal intra-atrial Wenckebach on distal atrioventricular nodal, and His-Purkinje, block

With special reference to the theory of alternating Wenckebach periods

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Most reports discussing alternating Wenckebach periods (AW) have referred to its occurrence in a single structure, generally the atrioventricular (A V) node[1-8] and less frequently the His Purkinje system[9-1] There have been only a few published examples of AW resulting from simultaneous involvement of two different structures which in the reported cases have been the two mentioned above [11-13] Therefore the purpose of this communication is to discuss the effects that a proximal intra atrial Wenckebach type of conduction disturbance can have on higher degrees of block occurring in more distally located structures placing special emphasis on the general theory of AW and of multilevel block

Material and methods

Electrophysiological studies were performed in eight patients after explaining the procedure and obtaining informed consent Drugs had been discontinued for at least 48 hours His bundle electrograms were obtained as previously outlined with a tripolar catheter electrode placed across the tricuspid valve[1] A hexapolar catheter electrode was also introduced through an antecubital vein to record or pace from the high right atrium, mid right atrium and right ventricular apex In six patients stimulation from high right atrium (at a distance of approximately 15 to 25 mm from the high right atrial electrode pair of the hexapolar catheter) was performed through a third catheter electrode, which in the early phase of the study had been placed inside the coronary sinus Interelectrode distance was 10 mm The programmed stimulator used delivered rectangular pulses of 2 msec duration and approximately twice diastolic threshold values

As in other laboratories part of the workup of our patients with recurrent supraventricular tachyarrhythmias includes attempts to induce A V reciprocating tachycardias as well as atrial flutter or fibrillation[15-17] This was attempted on two separate occasions in each patient by gradually increasing the pacing rate up to 300/minute

This report deals with the events occurring when these attempts resulted in a pattern suggestive of intra atrial Wenckebach as defined below

Definitions

HRA and MRA were the high right atrial and mid right atrial deflections recorded by the corresponding electrode pairs of the hexapolar catheter

LRA was the low right atrial deflection in the His bundle electrographic (HBE) lead

St was the pacemaker stimulus artefact

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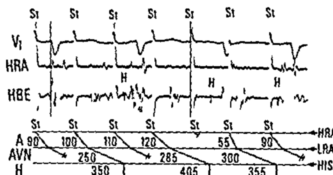


Fig 1 (Case 3) 2 1 St H block with coexisting proximal intra atrial Wenckebach and distal 2 1 A V nodal (LRA H) block Completion of the proximal Wenckebach cycle in the stimulus (fifth from the beginning of the strip) which was blocked (at the distal level) during the 2 1 St H sequence prevented the appearance of 3 1 St H block St = pacemaker stimulus artefact delivered to the high right atrium through the quadripolar catheter electrode *HRA = high right atrial electrogram recorded by the hexapolar catheter electrode* LRA = low septal right atrial electrogram recorded from the vicinity of the A V node (AVN) in the His bundle electrographic (HBE) lead *A* = atria *H* = His bundle Numbers at the A AVN (atrioventricular nodal) and H level indicate duration of St LRA LRA H and St H intervals respectively In this and all following figures values are expressed in msec

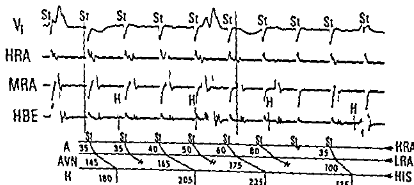


Fig 2 (Case 6) 2 1 St H block with coexisting proximal intra atrial Wenckebach and distal 2 1 A V nodal (LRA H) block Completion of the proximal intra atrial Wenckebach cycle in the stimulus which was conducted during the 2 1 sequence resulted in progression to 3 1 St H block.

The St LRA interval was used as a rough measurement of intra atrial conduction time (from paced HRA site to the vicinity of the A V node)

The LRA H and H V intervals were used to estimate A V nodal conduction time and His Purkinje conduction time respectively

The St H interval represented the conduction time through the atria (proximal level) and the A V node (distal level)

The St V interval included conduction time through the atria (proximal level) A V node (distal level) and His Purkinje system (distal level)

An intra atrial Wenckebach was an episode of progressive prolongation of St LRA intervals until one stimulus was not followed by a propagated response

A completed AW period[1-4] was an episode of 2 1 St H (or St V) block in which there was a prolongation in transmission intervals of conducted beats ending with two or three consecutive stimuli failing to reach the His bundle (or ventricles) that is with conversion of 2 1 into 3 1 or 4 1 St H (or St V) block

An abortive AW period was an episode of 2 1 St H (or St V) block in which the progressive prolongation in transmission intervals of conducted beats was interrupted or changed before progression into 3 1 block had time to occur

Results

In all patients intra atrial Wenckebach occurred at cycle lengths (210 to 275 msec) which were shorter than those at which 2 1 LRA H block had occurred (280 to 350 msec) When

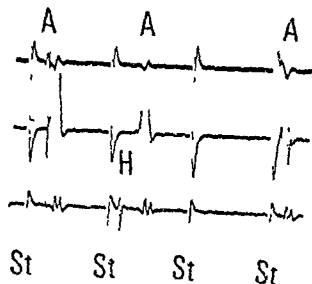


Fig 3 (Case 6) Enlargement of the part of *Fig* 2 which showed that the prolongation of the corresponding stimulus to response intervals occurred between the *pacing site and* closest recording electrodes From top to bottom high right atrial mid right atrial and low right atrial electrograms

HRA pacing was performed 15 to 25 mm from the closest (also HRA) recording electrodes it was observed that the gradual increase in the stimu lus response intervals occurred between pacing site and recording HRA electrodes (Figs 1 to 4) Therefore the time elapsing between inscription of HRA and MRA electrograms and between MRA and LRA electrograms was the same at all St St intervals

Six patients developed intra atrial Wencke bach during 2 1 St H block resulting from 2 1 A V nodal (LRA H) block (Table I) In four cases the stimulus which was not followed by a LRA deflection was that which had been blocked at the A V node (LRA electrogram not followed by H deflection) during the 2 1 sequence (Table I and Fig 1) Therefore, conversion to 3 1 block did not occur

Fig 1 also shows that while the intra atrial Wenckebach was occurring (at a pacing cycle length of 270 msec) there also was a gradual prolongation of St H intervals (abortive AW) manifested by an increase of St H intervals from 350 to 405 msec This abortive AW (due to delays at both, atrial and A V nodal levels) was modified by the completion of the intra atrial Wenckebach since the latter decreased the St H intervals from 405 to 355 msec

In two patients (Cases 5 and 6) the intra atrial Wenckebach ended with the stimulus which had been able to traverse the A V node during the 2 1 sequence (LRA deflection followed by H electro gram) This resulted in progression to 3 1 St H block

Fig 2 depicts an AW of St H interval (ending in two consecutively blocked stimuli) due to the coexistence of proximal (intra atrial) Wencke bach (manifested by a gradual increase of St LRA intervals) with distal (A V nodal) abortive AW (manifested by prolongation of LRA H inter vals during 2 1 LRA H block) This occurred while the pacing cycle length was decreased from 235 to 210 msec

In three patients the intra atrial Wenckebach appeared when the over all conduction pattern was that of 4 1 St V block (Table II) In one of the two patients with distal 4 1 A V nodal (LRA H) block (Case 7) the intra atrial Wenckebach was completed in a stimulus which would have been blocked (thereby maintaining the 4 1 ratio) but in Case 8 it terminated in the stimulus which would have been conducted The latter resulted in progression to 5 1 St H block (Fig 4) due to the documented existence of conduction disturbances in two different structures (atrial proximal, and A V node distal)

In one case the 4 1 St V block occurred because of alternation of 2 1 A V nodal (LRA H) block with 2 1 His Purkinje (H V) block (Fig 5) The intra atrial Wenckebach was completed in the stimulus which would have been conducted (when the pacing cycle length had been reduced from 250 msec to 220 msec) thereby resulting in progression into 5 1 St V block This was due to the documented existence of block in three different structures (atria, proximal, A V node distal and His Purkinje, distal)

Discussion

Mechanisms of gradual prolongation of St LRA electrograms The interval between a stim ulus delivered through a catheter electrode and an electrogram recorded by another catheter electrode comprises the time required for the local response to attain a sufficient intensity to allow propagation and the conduction time to the recording electrodes [22] The farthest the electrodes the greater the contribution of conduction time

In the six patients in whom HRA pacing was performed relatively close to the recording HRA electrodes the progressive delay in stimulus-re sponse intervals occurred in the vicinity of the stimulated site (Figs 1 to 4) Hence the propor

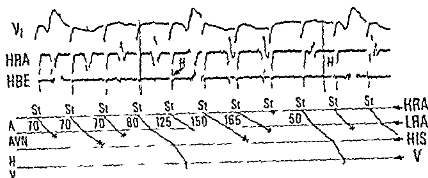


Fig 4 (Case 7) Proximal intra atrial Wenckebach during 4 1 St V block due to 4 1 A V nodal LRA H block. Completion of proximal Wenckebach cycle in a stimulus which could have conducted results in progression to 5 1 St V block Although only two levels of conduction impairment could be documented (atria and A V node) conventional electrocardiographic theory suggested a third (intra nodal) level. However the existence of the latter could not be proved even with His bundle recordings.

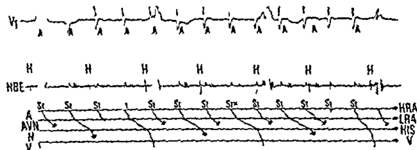


Fig 5 (Case 6) Proximal intra atrial Wenckebach during 4 1 St V block due to alternation of 2 1 A V nodal (LRA H) and 2 1 His-Purkinje (H V) block Completion of the proximal Wenckebach cycle in the stimulus which was conducted during the 4 1 sequence produced a progression in th degree of block (to 5 1) The latter resulted from documented three level block involving three separate structures (atria A V node and His Purkinje system)

tion with which true latency and slowed conduction around the pacing electrode contributed to the genesis of the intra atrial Wenckebach could not be determined with certainty[2] However in other cases with intra atrial disease the prolongation of the St LRA electrograms has occurred after the inscription of the HRA electrogram that is between the latter and the LRA electrogram

Because this phenomenon occurs within the atria several authors have suggested that the term intra atrial Wenckebach pattern can be applied from a descriptive point of view regardless as to its exact electrophysiological mechanism

A similar prolongation of stimulus to response intervals was observed in canine hearts by Lewis and associates[2] during stimulation of the muscle in the vicinity of the superior vena cava In one experiment (their Fig 8) the tracing showed an increase of the stimulus to response intervals (from 37 to 140 msec) before the development of 2 1 block at a pacing rate of 370/minute[23]

Drury[5] noted that the stimulus to response intervals were longer during 2 1 intra atrial block than when 1 1 conduction occurred when the rate was one half A similar phenomenon is known to occur at the A V node[2] Both have been attributed to the (concealed) intra atrial or A V nodal conduction of the apparently blocked stimuli[23]

Some authors have described Wenckebach or AW patterns presumably occurring in the atrial myocardium surrounding ectopic foci or pacing electrodes during spontaneous automatic atrial tachycardias and rapid atrial stimulation[2]

Patterns resulting from the occurrence of

Table I Clinical and electrophysiological information in patients developing intra atrial Wenckebach during 2 1 St H block (due to 2 1 A V nodal, or LRA H, block)

Case	*Age*	*Diagnosis*	*St LRA (control)*	*LRA H (control)*	*CL of 2 1 LRA H block*	*CL of IAW*	*Maximal St LRA*	*IAW completed in*	*Consecutively blocked St*	*Conversion 2 1 into 3 1 block*
1	53	RSVT	45	95	280	225	115	Blocked St	1	No
2	49	RSVT	60	115	370	270	120	Blocked St	1	No
3	67	RSVT PCSD	55	75	350	275	120	Blocked St	1	No
4	56	SSS	60	85	345	230	125	Blocked St	1	No
5	73	PCSD	55	105	305	215	105	Conducted	2	Yes
6	62	WPW PCSD RSVT	35	100	280	210	80	Conducted	2	Yes

RSVT = repetitive supraventricular tachyarrhythmia PCSD = primary conducting system disease SSS = sick sinus syndrome WPW = Wolff Parkinson White syndrome St = stimulus artifact LRA = low right atrium H = His bundle CL = cycle length IAW = intra atrial Wenckebach

Table II Clinical and electrophysiological information in patients developing intra atrial Wenckebach during 4 1 St V block

Case	*Age*	*Diagnosis*	*St LRA control*	*LRA H control*	*CL of 4 1 St V block*	*Type of 4 1 St V block*	*Cl of IAW*	*Maximal St LRA*	*Consecutive ely blocked St*	*IAW compl ted in*
7	66	PCSD RSVT	55	115	230 260	4 1 LRA H	225	115	4	Blocked St
8	59	PCSD SSS	75	95	240 260	4 1 LRA H	210	165	5	Conducted St
6*	62	WPW PCSD RSVT	55	105		2 1 LRA H alternating with 2 1 H V	210	80	[illegible]	Conducted St

Abbreviations as in Table I
* Same patient as in Table I but different attempt to induce atrial flutter or fibrillation

intra atrial Wenckebach during A V nodal (LRA H) 2 1 block Although Halpern and colleagues[9] consider that AW can be due to a single level of block most authors accept that it is due to two levels of block occurring generally in one structure[1 8 11 14]

Even with His bundle recordings the limits of the proximal and distal levels can only be surmised when AW occurs exclusively at the A V node (manifested by the corresponding variations of the LRA H intervals) or exclusively at the His Purkinje system (manifested by the expected changes of the H V intervals)[7 9 13]

In three previously reported cases of AW resulting from two levels of block occurring in two separate structures, the A V node and the His Purkinje system were involved but not the atria[7 11 13 20] These studies as well as the present communication support the two level block concept since the limits of the proximal and distal levels could be determined by the intracardiac electrograms

It is generally accepted that AW ending with two blocked impulses is due to the association of proximal Wenckebach with *distal (fixed) 2 1 block*[6 7 9] However Fig 2 shows that AW of St H intervals can also result from the coexistence of proximal and distal Wenckebach or AW cycles

Although this mechanism had not been proved with His bundle recordings Kosowsky and colleagues implied (using only the surface electrocardiogram) that Wenckebach cycles can be simultaneously present in both proximal and distal A V nodal levels In fact the ladder diagram below Fig 8 of the article by Kosowsky and colleagues depicts proximal 5 4 and 6 5 Wenckebach associated with distal 4 3 Wenckebach[4]

Patterns resulting from the occurrence of

Intra atrial Wenckebach during 4 1 St V block This study shows that a proximal intra atrial Wenckebach can occur during 4 1 St V block without increasing the degree of block provided that the cycle was completed in stimuli which would have been blocked during the 4 1 sequence However conversion of 4 1 into 5 1 did occur when the Wenckebach cycle ended within the stimuli which would have been conducted (Figs 4 and 5)

In the two patients in whom the 4 1 St V block was due to 4 1 A V nodal (LRA H) block (Fig 4) two levels of conduction impairment were demonstrated (atria and A V node respectively) In conventional electrocardiographic interpretations it is usually accepted that 4 1 A V nodal block can result from a two level block the upper level stopping every other impulse and the lower level stopping every other one which traversed the upper region[1] If this concept is correct the events depicted in Fig 4 can be attributed to a three level conduction disturbance involving two separate structures

Moreover 5 1 A V nodal block has been attributed to three level conduction disturbance[1] This assumption is supported by the findings in Fig 5 where 4 1 St V block (due to alternation of 2 1 A V nodal block and 2 1 His Purkinje block) progressed into 5 1 St V block when the intra atrial Wenckebach was completed in the stimulus which would have been conducted

Clinical implications A great number of assumptions used in present day electrocardiographic interpretation were originally made by deductive reasoning from clinical tracings Many have been corroborated by extrapolating information obtained from recording action potentials from the various components of the conducting system and by directly recording His bundle activity in man in conjunction with artificial pacing of atria and ventricles[12]

As mentioned previously the existence of multilevel block has been used for many years to explain a variety of commonly encountered arrhythmias Although the exact incidence of multilevel block at the A V node has not been determined with certainty Kosowsky and colleagues postulated that it could occur more often than suspected since they were able to identify 36 cases during a two year period in a 415 bed general community hospital[4] Kosowsky and colleagues considered it as a frequent usually transient conduction pattern which by itself had no short term detrimental prognostic implications On the other hand multilevel block at the His Purkinje system carries a bad prognosis insofar as A V conduction is concerned

It is thus evident that validation of the theory of AW (a manifestation of multilevel block) has a direct bearing on the diagnosis treatment and electrocardiographic recognition of commonly encountered arrhythmias

Summary

Intra atrial Wenckebach patterns of stimulus to response intervals coexisting with distal A V nodal and His Purkinje blocks occurred in eight patients during high right atrial stimulation at rapid rates In two patients with 2 1 St H block and in two patients with 4 1 St V block an increase in the degree of block occurred when the proximal intra atrial Wenckebach cycle was completed with the stimulus which otherwise would have been propagated to the distal levels However the degree of block did not increase when the intra atrial Wenckebach terminated in distally blocked stimuli In one patient progression of 4 1 into 5 1 St V block was due to the association of intra atrial Wenckebach with alternating 2 1 block at the A V nodal and His Purkinje levels

Contrasting with most reports dealing with the mechanisms of alternating Wenckebach in a single structure this study permitted the determination of the boundaries between proximal and more distal levels It also showed that alternating Wenckebach cycles (of St H intervals) ending with two consecutively blocked stimuli could result from the association of proximal intra atrial Wenckebach with distal A V nodal Wenckebach or abortive AW cycles

The electrophysiology of documented two or three level block in *different* structures has validated previously made assumptions regarding multilevel block in a *single* structure

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Case reports

Misdiagnosis of atrial septal defect in patients with hereditary telangiectasia (Osler-Weber-Rendu disease) and hepatic arteriovenous fistulas

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High output congestive heart failure secondary to arteriovenous malformations is a well recognized entity [1] Hereditary hemorrhagic telangiectasia (Osler Weber Rendu disease) is known to be associated with arteriovenous fistulas particularly of the lung Much less common is a hepatic arteriovenous malformation in combination with this disease [3] When such an uncommon malformation occurs it seldom produces a hyperkinetic circulation [*]

We wish to describe two patients who had Osler Weber Rendu disease and large hepatic arteriovenous malformations Initially both patients had signs and symptoms of congestive heart failure that were believed to be due to atrial septal defects and both underwent cardiac catheterization and exploratory cardiotomy

Case report

Case 1 A 46-year-old white woman was first seen at the Mayo Clinic on October ?8 19 1 Her chief complaints were exertional dyspnea occasional paroxysmal nocturnal dyspnea and anginal chest pains At th ag of 17 y ars she had been told of a heart murmur but she had no history of acute rheumatic fever or congenital heart disease She had multiple h mangiomas of the lips and tongue for many years with occasional episodes of bleeding She had experienced an episode of hematemesis in 19?9 and had had several transfusions.

On examination her blood pressure was 1?4/60 *mm Hg* with a regular pulse of 9? beats per minute Multiple telangiectatic lesions on the lips and tongue were noted Her precordium was hyperactive with the cardiac apex 2 to 3 cm to the left of the midclavicular line in the fifth intercostal space A Grade 5/6 holo ystolic murmur was heard loudest at *the left sternal border* but it was widely transmitted over the entire thorax and to the neck The second heart sound split normally and there was no diastolic murmur A presystolic gallop was recorded Also noted was an *enlarged nonpulsating* liver

The hemoglobin level was 6 8 Gm /dl with a normal leukocyte count A platelet count was 563 000/mm with a reticulocyte count of 1 7 *per cent* The sedimentation rate was 44 mm in 1 hour The serum iron level was ?3 μg/dl (9 per cent saturation) and a blood smear demonstrated changes consistent with chronic blood loss Fluoroscopic views of the heart showed cardiac enlargement with mild biventricular enlargement and enlargement of the left atrium There was an increase *in the intensity* of the aortic pulsations both in the ascending and the descending aorta Electrocardiogram revealed a rate of 90 beats per minute with sinus arrhythmia and voltage *criteria for left* ventricular hypertrophy The following were normal urinalysis haptoglobin levels stools for occult blood *test of renal* function and a roentgenogram of the stomach

While hospitalized the patient was transfused with packed red blood *cells and her* hemoglobin level increased to 11 2 Gm./dl. Results *of cardiovascular* examination were unchanged despite the increase in hemoglobin concentration Clinically *the loss of blood* was considered to be due to bleeding from *hemangiomas* within the gastrointestinal tract. Because of the uncertain cardia diagnosis and her primary complaints she underwent cardiac catheterization on November 4 19 1

Double-dye sampling *(Fig 1) and* hemodynamic data and oxygen saturations (Table 1) suggested a large left to-right shunt presumed to be *at* atrial level. Abnormal pressure elevations (Table 1) *consistent with* long-standing left to right shunting and volume overload were observed However the clinical findings did *not entirely* support the findings of atrial

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Fig 2A (Case 1) Preoperative hepatic angiogram Selective common hepatic injection demonstrates very large right and left hepatic arteries with high volume flow



Fig 2B (Case 1) Two and one half seconds after *Fig 2A* was made the hepatic vein *(arrows)* can be visualized because of rapid intrahepatic shunting

Postoperatively careful examination revealed a bruit over the liver On December 16 1971 selective hepatic and superior mesenteric arteriograms revealed a large vascular anomaly in the right and left lobes of the liver (Fig) along with arteriovenous malformations in the duodenum

The patient returned to our clinic in January with severe limitation in activity and progression of exertional dyspnea orthopnea and ankle edema

On February 10 1972 the hepatic artery was ligated proximal to its gastroduodenal branch Flow through the right hepatic artery determined by electromagnetic flowmeter was 2,350 ml /min before ligation with a reduction to 400 ml / min after ligation Flow in the hepatic artery proximal to its bifurcation was 4 000 ml /min before ligation and diminished to 1 000 ml./min after ligation Hemodynamic studies (Table I) along with postoperative superior mesenteric and celiac axis arteriograms (Fig 3) performed on March 9 1972 showed a considerable reduction in the left to right shunt The patient was dismissed from the hospital on March 1? 19/2

Case 2 A 37 year-old white woman was first seen at the Mayo Clinic on August 6 1975 Her primary complaints included recurrent nausea and vomiting associated with a low grade fever and a decrease in hemoglobin concentration to below normal The symptoms had their onset in July 19/4 Repeated attempts to localize a site of bleeding were unsuccessful.

At the age of 7 years, the patient was severely anemic and she retained a mild persistent iron-deficiency anemia most of her adult life despite regular iron therapy Her father had hereditary hemorrhagic telangiectasia with numerous bleeding episodes from the nose and gastrointestinal tract In March, 19"1 she was noted to have cardiomegaly and a diagnosis of su pected congenital heart disease was made In June 19 4 she underwent cardiovascular evaluation because of the persi tent cardiomegaly exertional dyspnea and nonradiating chest pain Examination at that time revealed a



Fig 2C (Case 1) Preoperative hepatic angiogram made 4.5 seconds after Fig ?A Right and left hepatic veins are easily identified

bounding heart with a Grade 2/6 murmur heard best at the upper left sternal border Findings were reported to be consistent with aortic stenosis The electrocardiogram showed evidence of left ventricular hypertrophy and the chest roentgenogram showed changes consistent with a large left to right shunt

Cardiac catheterization on June 6 1974 demonstrated a superior vena cava oxygen saturation of 74 per cent right atrial, right ventricular and pulmonary artery saturation of 87 per cent and systemic arterial saturation of 95 per cent Intracardiac pressures were normal. The findings were consis

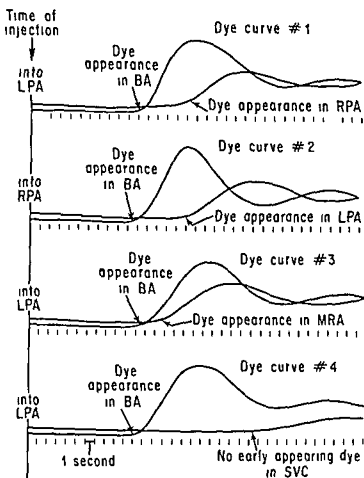


Fig 1 (Case 1) Preoperative dye curves Selected dye curves with indocyanine green injections into right and left pulmonary arteries and sampling at central and peripheral sites No sampling was done at level of inferior vena cava *Dye curve 1* When dye was injected into left pulmonary artery *(LPA)* and continuous samples were taken from the brachial *(BA)* and right pulmonary arteries *(RPA)* dye appeared in RPA *(arrow)* too early (relative to the brachial artery curve) to be accounted for by normal recirculation This is suggestive of left to right shunt to some systemic vein or right heart chamber upstream to pulmonary arteries *Dye curve 2* Similar to Curve 1 except that the pulmonary artery dye injection and sampling catheters were reversed Early dye is now seen in left pulmonary artery *(LPA)* excluding possibility of isolated anomalous pulmonary venous return *Dye curve 3* With central sampling catheter withdrawn to right atrium *(MRA)* dye injected into left pulmonary artery *(LPA)* again appeared early in MRA *(at arrow)* indicating that the right atrium is at or still downstream to site of right to left shunt *Dye curve 4* In contrast to Curve 3 dye injected into left pulmonary artery *(LPA)* did *not* appear early in central sampling catheter which was placed in superior vena cava *(SVC)* These curves demonstrate that the superior vena cava is upstream to site of left to right shunt and suggest that this shunt drains into right atrium—a pattern usually seen in atrial septal defects A potential central site of left to right shunt was the inferior vena cava and this could have been excluded by a central sample curve obtained from this site which showed no early appearing dye Absence of abnormally elevated oxygen saturation (which should occur with shunting of arterial blood) in the inferior vena cava below the diaphragm was considered to exclude this possibility (see Table I)

Table I Catheterization data in Case 1*

Site	Preoperative (Hb = 9 4 Gm./dL)		Postoperative (1 mo) (Hb = 8 2 Gm /dL)	
	Pressure (mm Hg)	Saturation (%)	Pressure (mm Hg)	Saturation (%)
Brachial artery	140/72	95	140/70	97
Left ventricle	155/17 28	–	–	–
Wedge	30/21 29	95	14/8	9
Pulmonary artery	68/30	84	34/15	83
Right ventricle	75/14	83	39/1	–
High right atrium	–	72	–	80
Mid right atrium	21/10	87	11/3	80
Low right atrium	–	86	–	80
Inferior vena cava (below diaphragm)	–	69	–	[illegible]
Superior vena cava (high)	–	63	–	79
Superior vena cava (low)	–	66	–	80
Calculations†				
	Qs = 4 9 L /min = 3 1 L /min /M²		Qs = 9 5 L./min = 6 0 L /min /M²	
	Qp = 11 5 L./min = 7 2 L /min /M²		Qp = 11 8 L /min = [illegible]4 L /min /M²	
	Qp/Qs = 2 3 1		Qp/Qs = 1 ? 1	
	Left to right shunt = 60%		Left to right shunt = 20%	

*Note on preoperative data that both IVC and SVC O saturation data are within normal limits but a marked increase in O saturation occurred at level of right atrium Preoperative saturation data are consistent with the dye dilution data suggesting left to right shunt at the atrial level Postoperative catheterization data indicate a marked reduction in pulmonary wedge pulmonary arterial, and right ventricular pressures in addition to reduction in left to right shunt to one third of preoperative values

†Qs = systemic flow Qp = pulmonary flow

septal defect Moreover the early appearing central dye indicative of left to right shunt was somewhat delayed for shunting to be occurring directly across the atrial septum Because of the patient s hereditary telangiectasia a second cardiac catheterization was performed on November 10 1971 in an attempt to exclude the possibility of a left ventricular aortic root (sinus of Valsalva) or coronary arterial shunt to the right atrium The left ventricular and coronary angiograms revealed no abnormalities and dye curves from the aortic root and left ventricle excluded these possibilities Attempts to cross the septal defect were unsuccessful Once again an oxygen saturation step up was noted at right atrial level

The patient underwent exploratory cardiotomy on December 1 1971 and complete intracardiac inspection failed to reveal any abnormality although a systolic thrill was noted over the left atrium The surgical team noted oxygen-enriched blood returning from the inferior vena cava persistently throughout the operation and it was assumed that the left-to-right shunt was below the diaphragm

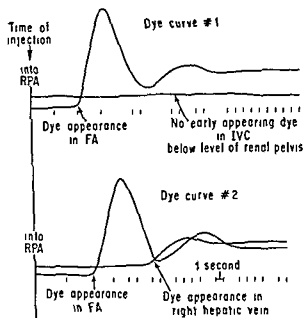


Fig 4 (Case 2) Preoperative dye curves Selected indocyanine green dye curves obtained at central and peripheral sampling sites (femoral artery = *FA*) after dye injection into right pulmonary artery *(RPA)* In addition to usual series of double sampling dye dilutions performed in patients with intracardiac shunts two additional central venous sites were sampled that demonstrated subdiaphragmatic suprarenal extracardiac location of left to right shunt *Dye curve 1* No early appearing dye was seen in inferior vena cava *(IVC)* below level of renal pelvis indicating no significant left to right shunting in systemic circulation peripheral to this sampling site *Dye curve 2* In contrast to dye curve 1 curve 2 shows indocyanine green dye appearing too early in right hepatic vein to be accounted for by normal systemic circulation indicating a left to-right shunt upstream of hepatic vein

was recognized as having an abdominal bruit that could have drawn attention to the presence of an intrahepatic fistula Clinical cardiovascular examination of either patient was not entirely consistent with atrial septal defect but the combination of heart failure and a hyperdynamic circulation raised enough suspicion of a valvular or intracardiac shunt lesion that cardiac catheterization was performed Because of the step up in oxygen saturation at the atrial level and the demonstration of left to right shunting typical of atrial septal defect by central and peripheral indocyanine green dye sampling curves it was assumed that the patients had atrial septal defect with an atypical presentation At operation however no cardiac disease was demonstrated and because of oxygen-enriched blood returning from the inferior vena cava the strong possibility



Fig 5A (Case 2) Hepatic angiogram Selective common hepatic injection preoperatively demonstrates very large right hepatic arteries with high flow



Fig 5B (Case 2) Hepatic angiogram Rapid intrahepatic shunting allows dense opacification of right hepatic veins *(single arrows)* and inferior vena cava *(double arrowheads)*



Fig 3 (Case 1) Postoperative superior mesenteric angiogram After common hepatic ligation injection into superior mesenteric artery demonstrates reduction in size of vessels to liver with filling via pancreaticoduodenal arcade to gastro duodenal artery *There has been a considerable reduction in* shunt volume

tent with an atrial septal defect and a pulmonary flow approximately 2 6 times greater than the systemic flow

The patient was referred for closure of the atrial septal defect and underwent exploratory cardiotomy on June 21 1974 However no intracardiac disease was demonstrated The surgeons reported bright red blood coming from the inferior vena cava and concluded that the left to right shunt was below the diaphragm Later an aortogram demonstrated a massive arteriovenous fistula in the liver

Examination at our clinic revealed a blood pressure of 110/70 mm Hg with a regular pulse of 80 beats per minute The patient s height was 62 4 inches (158 5 cm) and weight 147 lb (66 7 Kg) She had multiple small telangiectatic lesions on the lips and tongue

A right ventricular lift with a normal apical impulse was noted The first and second heart sounds were normal A prominent diastolic gallop was heard along the left sternal border A machinery type murmur was present along the sternum with wide radiation but was most prominent over the xiphoid region and right upper quadrant

The hemoglobin level was 12 6 Gm /dl with normal red blood cell indices platelets and leukocyte count Results of iron studies were also normal The electrocardiogram showed increased QRS voltage consistent with left ventricular hypertrophy and a nonspecific T wave abnormality A chest roentgenogram revealed cardiomegaly with increased peripheral pulmonary vascularity Results of renal and liver function tests were normal

Catheterization on August 18 1975 documented the degree of left to right shunting and identified the presence of the arteriovenous malformation A left to right shunt of 68 per cent was documented at the hepatic vein level (Table II) and selective indocyanine green dye curves confirmed the location of the shunt (Fig 4) *Injection into the hepatic vessels*

Table II Catheterization data in Case 2*

	Preoperative (Hb = 14 0 Gm /dl)		*Postoperative (3 wk) (Hb = 1[illegible]2 Gm /dl)*	
Site	*Pressure (mm Hg)*	*Saturation (%)*	*Pressure (mm Hg)*	*Saturation (%)*
Femoral artery	146/67	94	1[illegible]/72	94
Pulmonary artery	41/21	88	33/14	85
Right ventricle	45/6-15	88	–	–
High right atrium	–	75	–	–
Mid right atrium	13/7	87	12/6	87
Low right atrium	–	86	–	–
Inferior vena cava (at diaphragm)	–	*83*	–	8[illegible]
Inferior vena cava (upper pole of kidney)	–	73	–	86
Right hepatic vein	–	88	–	89
Superior vena cava	–	69	–	73
Calculations†				
Qs = 3 8 L./min = 2 3 L /min /M²			Qs = 7 1 L./min = 4[illegible] L /min /M²	
Qp = 10 5 L /min = 6 2 L /min /M²			Qp = 9 4 L /min = 5 5 L./min /M²	
Qp/Qs = 2 7 1			Qp/Qs = 1 3 1	
Left to right shunt = 68%			Left to right shunt = 38%	

Note increased oxygen saturations in low right and mid right atrium similar to those obtained in Case 1 In this case however because of *prior experience with this disease entity* and the operative findings before catheterization selective sampling from the right hepatic vein and at multiple levels in the inferior vena cava was performed
†Qs = systemic flow Qp = pulmonary flow

demonstrated a pronounced increase in flow with rapid arteriovenous shunting and dense filling of the hepatic veins and inferior vena cava (Fig 5)

On August 25 1975 the common hepatic artery was ligated proximal to the gastroduodenal branch *This reduced the flow* of blood determined by electromagnetic flowmeter from 800 to 230 ml /min

Postoperative catheterization on September 9 1975 demonstrated a reduction of left to right shunting at hepatic vein level to 38 per cent (Table II) A hepatic arteriogram (Fig 5) revealed that the shunting in the liver was reduced although substantial shunting remained via collateral vessels arising from the superior mesenteric artery

The patient was dismissed from the hospital *on September* 10 1975 Eight months after operation she has remained asymptomatic and has had no recurrence of her bleeding episodes.

Discussion

Both patients had Osler Weber Rendu disease When seen initially with symptoms of heart failure and cardiac abnormalities neither patient

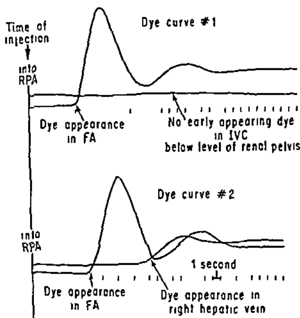


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Table II Catheterization data in Case 2*

Site	*Preoperative (Hb = 14 0 Gm /dL)*		*Postoperative (3 wk) (Hb = [illegible] Gm /dL)*	
	Pressure (mm Hg)	*Saturation (%)*	*Pressure (mm Hg)*	*Saturation (%)*
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Pulmonary artery	41/21	88	33/14	[illegible]
Right ventricle	45/6-15	88	–	–
High right atrium	–	75	–	–
Mid right atrium	13/7	87	[illegible]/6	[illegible]
Low right atrium	–	86	–	–
Inferior vena cava (at diaphragm)	–	83	–	[illegible]
Inferior vena cava (upper pole of kidney)	–	73	–	86
Right hepatic vein	–	88	–	89
Superior vena cava	–	69	–	[illegible]

Calculations†

Preoperative	Postoperative
Qs = 3 8 L /min = 2 3 L /min /M²	Qs = 7 1 L /min = [illegible] L /min /M²
Qp = 10 5 L /min = 6 2 L /min /M²	Qp = 9 4 L /min = 5 5 L /min /M²
Qp/Qs = 2 71	Qp/Qs = 1 31
Left to right shunt = 68%	Left to right shunt = 38%

Note increased oxygen saturations in low right and mid right atrium similar to those obtained in Case 1 In this case however because of prior experience with this disease entity and the operative findings before catheterization selective sampling from the right hepatic vein and at multiple levels in the inferior vena cava was performed
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Discussion

Both patients had Osler Weber Rendu disease When seen initially with symptoms of heart failure and cardiac abnormalities neither patient

vein and superior vena cava to provide shunt localization and a second method of quantification of shunt size. Dye injected into the pulmonary artery also should be sampled in stepwise progression along the venae cavae and ideally in the hepatic vein. In our two reported cases either the omission of a central dye curve from the inferior vena cava downstream from the hepatic veins or the obtaining of an oxygen sample from the inferior vena cava *upstream* of the hepatic veins accounted for the failure to recognize the level of the left to right shunt at cardiac catheterization. If a surgical procedure is performed postoperative catheterization should be done to assess the effects of surgery designed to reduce the magnitude of the left to right shunt.

In 1964 Graham and associates described a patient with familial hereditary telangiectasia and hepatic artery aneurysm who had portal vein fistula. High output congestive heart failure was controlled by the surgical removal of the large shunt but the patient died of recurrent bleeding and liver failure. DeLorimier and colleagues[1] later reviewed the natural history of symptomatic hepatic capillary hemangioma and emphasized the aggressive course of these lesions pointing out that most patients die from progressive heart failure. They described one patient in whom the main hepatic artery was ligated in order to diminish the large hepatic arteriovenous fistula. The patient experienced relief of heart failure and recovered. A limited number of other patients with congenital intrahepatic arteriovenous fistulas and hepatic artery portal vein fistulas have been treated by surgical means with satisfactory results. Everhart described a patient similar to our two who initially was considered to have heart failure secondary to rheumatic heart disease. Subsequent catheterization and angiography demonstrated a large hepatic arteriovenous fistula. The patient was successfully treated with ligation of the common hepatic artery.

Both of our patients underwent operation in an attempt to reduce the size of their large left to right shunts and to relieve some of the cardiac burden. Each patient had a sizable reduction in the shunt after the operation although the second patient had substantial residual shunting via collateral vessels as demonstrated by hepatic angiography.

Although at 3 and 4 weeks after operation the left to right shunting was found to be reduced significantly in our two patients limited experience with this problem would indicate that later recurrence of arteriovenous fistulas is probable owing to collateral arterial resupply.

Summary

Two patients with hereditary telangiectasia (Osler Weber Rendu disease) and high output congestive heart failure secondary to large hepatic arteriovenous malformations had preoperative heart catheterization and exploratory cardiotomy to correct presumed intracardiac left to right shunts at the atrial level. At operation both patients had oxygen-enriched blood returning from the inferior vena cava. Subsequent hepatic angiography demonstrated large hepatic arteriovenous fistulas and both patients underwent hepatic artery banding and ligation with reduction of left to right shunting.

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Fig 5C (Case 2) Postoperative study after ligation of common hepatic *(arrow)*



Fig 5D (Case 2) Hepatic angiogram Flow is now via pancreaticoduodenal arcade *(arrows)*

of an arteriovenous fistula below the diaphragm was recognized

Recently two patients with Osler Weber Rendu disease and hyperkinetic circulation secondary to intrahepatic fistula have been described[8 9] Both patients had signs and symptoms of congestive heart failure as well as hepatomegaly with abdominal bruits Chest roentgenograms revealed pulmonary plethora in both and cardiomegaly in one[8] The electrocardiograms showed only repolarization changes Each patient underwent cardiac catheterization liver biopsy, and hepatic angiography The liver biopsy in one



Fig 5E (Case 2) Hepatic angiogram Superior mesenteric injection demonstrates filling of markedly reduced intrahepatic shunts via pancreaticoduodenal to gastroduodenal vessel route *Arrow* denotes point of banding of gastroduodenal artery

patient was obtained during laparotomy that was performed to identify a source of recurrent bleeding Before catheterization both patients were suspected of having extracardiac shunts Hence a hepatic vein sample was obtained at catheterization from each patient and both patients demonstrated a marked step up in oxygen saturation at that level One patient was treated with a cardiotonic regimen and careful clinical supervision No remarks about treatment were made concerning the second patient

The combination of Osler Weber Rendu disease large intrahepatic arteriovenous malformations and high output heart failure is rare However in any patient with this disease and symptoms of cardiac failure a careful search must be made for bruits and other signs of arteriovenous fistula that may be responsible for the heart failure Halpern and colleagues[1] demonstrated the useful role of angiography in delineating these lesions particularly in the abdominal viscera Even in the presence of an arteriovenous malformation cardiac catheterization should be performed to determine the possible coexistence of cardiac abnormalities and to measure the magnitude of the shunt Blood samples for oxygen saturation should be taken in stepwise fashion in the inferior vena cava hepatic

Pulmonary varix Report of a case with additional anomalies of the vascular pulmonary tree

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E Marin
A Sanchez
J Solozabal
Madrid Spain

Pulmonary varix is a rare benign vascular anomaly It consists of a localized dilatation of one or more pulmonary veins that end normally in the left atrium Its radiological appearance prompts us to rule out other similar looking disease processes such as granulomatous diseases solitary pulmonary nodule lung carcinoma hilar lymph node diseases and pulmonary A V fistula

The first case was described by Puchet in 1843 as an autopsy finding[1] The following five cases were also found in postmortem examinations Clinically it was first diagnosed by Mouquin and associates in 1951 by means of angiography

Until now there have been 40 published cases[1] This report presents a new case with additional anomalies of the pulmonary vascular tree

Case report

A 21 year old female was admitted to this Hospital because of intermittent headaches At the age of 4 years a right hilar mass was accidentally encountered The review of systems family and past history and physical examination were unremarkable Laboratory examinations including ECG EEG and skull x rays were normal In the routine chest x ray a round mass was evident in the right hilum (Figs 1 and 2) At fluoroscopy its size and radiological density seemed to change with respiration and the Valsal a maneuver

The suspicion of its vascular origin was ascertained by means of catheterization and right pulmonary artery angiography Blood gas analysis and pulmonary pressures were

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Fig 1 Frontal chest x ray A round mass is evident in the right hilum

within normal limits The arterial phase showed a hypoplastic right superior lobar artery (Fig 3) and the hilar mass was not opacified However it appeared during the venous phase simultaneously with the pulmonary veins left atrium and ventricle and before the aorta thus excluding any anomalous blood supply to the lung from aortic origin (Fig 4) The right superior lobar vein was absent and the dilated right inferior lobar vein corresponded exactly with the detected mass in the simple chest x ray All these findings confirmed the diagnosis of pulmonary varix

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monary disease must be sought for Hemoptysis is an important finding that may or may not be related to the varix itself In four cases pulmonary tuberculosis and bronchiectases were associated[2,3,4,5] Seven other cases presented mitral valvular disease[9,1 20,2 23] The relation of pulmonary varix to the severity and duration of the venous hypertension is not clear since varices are rare as compared with the incidence of mitral disease On the other hand the operative treatment of the latter did not change in many cases the radiological aspect of the varix suggesting that the venous hypertension acts only as a predisposing or aggravating factor[1 1 2]

The reported case presented in addition to the varix a hypoplastic right superior pulmonary artery and an absent right superior pulmonary vein The venous drainage into the left atrium came trough a single inferiorly located pulmonary vein Similar cases have been described by Arnett and Patton[1] Papamichael and colleagues[3] reported the association of right pulmonary varix with absence of right superior pulmonary vein and diaphragmatic eventration The association of varices with patent ductus ventricular septal defect double outlet right ventricle anomalous pulmonary venous return with pseudocoarctation of the aorta and Klippel Trenaunay Weber syndrome has also been reported[2 2]

The differential diagnosis includes pulmonary vascular malformations granulomatous diseases benign and malignant bronchopulmonary tumors mediastinal tumors lymph node disease processes and cysts Fluoroscopy and tomography may help to separate vascular from non vascular masses especially when the diagnosis of A V fistula is contemplated However pulmonary angiography is the best procedure to make a diagnosis without having to recur to surgery Bartram and Strickland in 1971 described the angiographic criteria necessary for the diagnosis of pulmonary vein varix (1) normal arterial phase of pulmonary angiography (2) opacification of the varix at the same time as the pulmonary veins (3) slow drainage into the left atrium (4) dilatation and tortuosity of the proximal vein with normal distal branches

The natural history of the pulmonary varix is not known The prognosis is good in young symptomless individuals no increase in size has been observed in several years of follow up[15 2] In those with venous hypertension its size tends to augment[14] There are two main complications systemic embolization and fatal rupture into the pleural space or into a bronchus[4 27]

Regarding its treatment the cases discovered accidentally only need annual radiographic control Those related to cardiac processes may if the lesion expands be treated surgically correcting the cause of the venous hypertension and repairing the vein

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Fig 2 Lateral chest x ray Another view of the mass visualized in *Fig 1*



Fig 3 Arterial phase of pulmonary angiography showing a hypoplastic right superior lobar artery



Fig 4 Venous phase of right pulmonary angiography The superior lobar vein is absent and the dilated inferior lobar vein is opacified corresponding with the detected mass in the simple chest x ray

Discussion

Pulmonary varix is an extremely rare entity of unknown origin When it is found in symptomless individuals it is considered to stem from alterations in the development of the primitive splanchnic plexus [17] In symptomatic patients with sustained pulmonary venous hypertension the varicosities were attributed to the venous hypertension [17 19]

Its rate of presentation is unknown since generally it produces no symptoms Most of the cases were diagnosed between the fourth and sixth decades the ages ranging from 7 to 65 years [13]

Pulmonary varix usually presents as a single mass though occasionally they are multiple having been reported in both lungs and anywhere within the lungs The right upper pulmonary lobe is the commonest site of location [8 14 15 20 21] The masses are symptomless otherwise a cardiopul

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DR RIAZ A AKHTAR A 28 year old white female electrocardiographic technician was admitted to Lankenau Hospital on December 26 1974 for refractory congestive heart failure

She was born in Poland but resided as a child in Argentina from 1957 to 1961 Her father had been treated for refractory supraventricular arrhythmia associated with left anterior hemiblock

In the fall of 1970 a routine ECG showed LBBB (Fig 1) The patient was asymptomatic until early 1972 when she complained of shortness of breath on exertion ankle swelling and fatigue The patient was admitted to the cardiac care unit with a heart rate of 30/minute and a high grade AV block The management included diuretics digitalization and the insertion of a permanent ventricular pacemaker with a demand rate of 60 pulses per minute (PPM) The patient was asymptomatic during the next two years but she returned to have the original demand pacemaker replaced by an atomic mode pacemaker (Model Medtronic No 9000) rate 74 PPM because of battery depletion of the original unit One month after atomic pacemaker replacement she noticed ankle edema shortness of breath and severe fatigue and palpitations A few weeks prior to the onset of symptoms she had an upper respiratory infection

On June 18 1974 cardiac catheterization revealed severely impaired left ventricular function LVEDP of 13 to 25 mm Hg normal coronary arteries and moderate mitral insufficiency resulting from mitral valve prolapse The pressures were AO = 84/58 mm Hg LV = 84/13 to 25 mm Hg peak dp/dt LV = resting 820 mm Hg/second and after exercise 730 mm Hg/second The electrocardiogram showed atrial flutter with high degree AV block and a ventricular rate controlled by the pacemaker at a rate of 74 PPM A sequential multiple analyzer of 12 vital determinations and a complete blood count on June 17 1974 were normal The immunoblobulins were as follows IgG = 135 mg per cent (normal 600 to 1300) IgA = 115 mg per cent (normal 50 to 300) IgM = 175 mg per cent (normal 50 to 250) A normal lipoprotein pattern was present The rheumatoid factor and antinuclear antibodies were negative A 2+ albumin was noticed in the urine with a specific gravity of 1017

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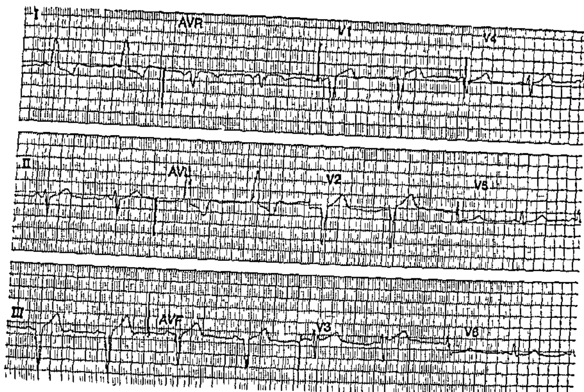


Fig 1 Electrocardiogram made in the fall of 1970 showing LBBB

tion Abdominal examination revealed the liver with a round firm edge of four fingerbreadths below the right costal margin Laboratory studies included a cholesterol of 120 mg per cent blood glucose of 160 mg per cent, bilirubin of 2 4 mg per cent, and hemoglobin 13 0 Gm The electrocardiogram showed atrial flutter, high grade AV block, and an electronic pacemaker rate of 74 PPM The chest x-ray showed a progressive increase in cardiomegaly since her past admissions, bilateral pleural effusions and a possible pericardial effusion An echocardiogram confirmed the pericardial effusion and suggested the amount was approximately 260 ml (Fig 2) Despite management with bed rest diuretics fluid restriction, her clinical progress was rather discouraging

On January 9 1975 an acute pulmonary embolism was suspected and was confirmed by lung scan Heparin was started but had to be discontinued because the partial thromboplastin time rose from 34 to 106 seconds with a small dose of 5000 units Ecchymosis and diffuse petechiae were noted over all regions of her body A hematological survey for disseminated intravascular coagulation was negative A gum biopsy was negative for amyloid The patient developed a spiking temperature of 103° F However repeated cultures of blood sputum, and urine failed to reveal any organism Evaluation for a leak of radioactivity proved negative

Clinical deterioration continued with fever refractory congestive heart failure cardiomegaly and subsequent pulmonary emboli The hemoglobin dropped progressively to 8 4 Gm on February 7 1975 and the white blood count increased to 26,000 The bilirubin was 3 5 mg per cent, SGOT 250 units, LDH 600 units and alkaline phosphatase was 175 units The patient became comatose on February 6, 1975 and died on February 7, 1975

DR DAVID H SPODICK I would be particularly interested to see an ordinary chest film and films of any other structures, for example the hands I would also be interested in actually examining the cineangiograms and the other catheterization data

DR ARTHUR PRESS Serial chest radiographs show progressively increasing heart size congestive changes and finally pulmonary and pleural abnormalities leading to demise Admission chest x ray on June 11, 1974 (Fig 3) exhibits mild to moderate general cardiac enlargement including left atrial fullness and minimal increased upper lung perfusion A transvenous atomic model pacer is positioned in the right ventricle Four months later the heart size is increased and there is slightly greater passive pulmonary congestion along with suggestive ascites as judged by loss of the postero inferior liver angle and separation of the lateral ascending

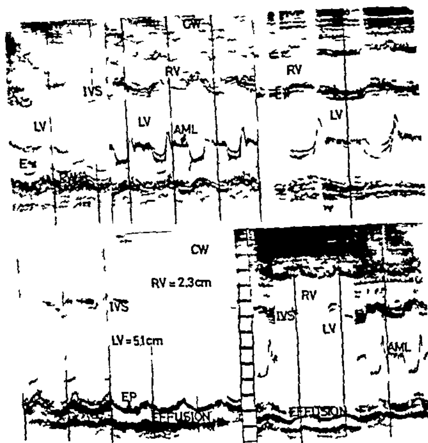


Fig 2 Echocardiogram CW = chest wall RV = right ventricle LV = left ventricle IVS = intraventricular septum AML = anterior leaflet of the mitral valve EP = posterior endocardium

colon contour from the adjacent properitoneal fat At the second admission on December 27 1974 the heart is still more globular in shape Pericardial fluid is a possibility but general chamber dilatation can account for the findings Subpulmonic effusions have developed along with the mild passive pulmonary changes On the fourteenth hospital day (January 10 1975) dramatic pulmonary opacities are seen (Fig 4) The entire left lower lobe is consolidated and a small quantity of pleural fluid is identified on a decubital film Two peripheral nodular lesions about 2 5 cm in size are seen in the right lung While the left lung process is nonspecific the right lung pleural base opacities suggest embolic phenomena

Dr Spodick Let us now examine the protocol for individual clues and diagnostic giveaways She was born in Poland but lived for many years in Argentina One thing that is common to both places is echinococcosis (Argentina has Chagas Disease but this usually produces RBBB and this patient had LBBB) The electrocardiogram later shows left axis deviation as well as LBBB Further analysis shows a QRS axis of −40 degrees The P waves are not unusual

She was apparently well for a few years and then presents with congestive heart failure and complete AV block with a ventricular rate of 30 beats per minute She might well have had one or more murmurs (owing to large stroke volume and progression of disease) but no murmurs are described at that time No third heart sound was heard which is unusual in the presence of advanced structural and functional cardiac abnormality In the presence of LBBB the first heart sound should have been of poor quality and the second heart sound might have split paradoxically but these were not described The protocol does not mention lymphadenopathy a sign of widespread diseases like lymphoma Hence the disease process may well have been limited to the



Fig 3 Chest x ray made on June 17 1974 First admission chest x ray shows mild to moderate globular cardiac enlargement minimal blood flow cephalization and a right ventricular pacemaker



Fig 4 Chest x ray made on Jan 10 1975 second hospitalization 14th day Extensive left lower lobe consolidation, minimal effusion and two poorly marginated peripheral right lung nodules The heart is larger and more globular but its base has not widened appreciably

mediastinum and lungs X ray films of the hands did not reveal findings which could have pointed to sarcoid or the connective tissues disease group The presence of upper respiratory infection (URI) may or may not have been significant in the subsequent events frequently a URI is a red herring In 1974 she had a cardiac catheterization May I see the data?

DR A N MOGHADAM Cardiac catheterization consists of left ventriculography left heart catheterization and coronary cineangiography The end diastolic pressure of the left ventricle was 24 mm Hg The systemic pressure was 84 mm Hg in the aorta and left ventricle There was dysfunction of the left ventricle and prolapse of the mitral valve There was some mitral insufficiency seen on the ventriculogram which could be due either to papillary muscle dysfunction or to asynchronous activation of the atria and ventricle in the presence of the permanent pacemaker The tracing is a square root form with a sudden termination of filling and a plateau No pericardial effusion is seen at the time of catheterization

DR SPODICK Catheterization has settled a number of questions There is a decreased dP/dt a poorly functioning dilated left ventricle and mitral insufficiency, as expected despite the absence of a murmur

The sequential multiple analyzer of 12 vital determinations at that time was normal including notably a normal serum albumen Both rheumatoid factor and antinuclear antibody titers are negative The 2+ albumin in the urine may be explained by congestive heart failure Study shows decreased IgG That reduction can be due to decreased synthesis, increased catabolism or both The lipoprotein pattern is normal

What do the bedside findings tell us? The patient developed increasing congestive heart failure and begins a rapid downhill course characterized by mainly right sided circulatory congestion without definite findings indicating left heart failure (You must have right heart 'success' to exhibit left heart failure) Pericardial effusion with cardiac tamponade for example could be a cause of systemic venous congestion and indeed there was considerable venous distention and the echocardiogram indicated some pericardial fluid Now for the first time in this seriously ill young woman a systolic murmur is mentioned Specifically a Grade 2/6 murmur at

the left lower sternal border which increased with expiration If this observation was accurate and if that was not a pericardial rub (which in about 30 per cent of patients can be louder on expiration) we can imagine rather odd causes such as tricuspid valve prolapse since the right ventricle would underfill during expiration The liver and neck veins did not pulsate which would have been expected for tricuspid regurgitation Ordinary tricuspid valvular incompetence by contrast produces louder murmurs in inspiration Another possibility is right ventricular obstructive cardiomyopathy with this type of expiratory exacerbation of the murmur although that would be an equally odd cause The murmur could have been due to an angulated jet effect from a mitral prolapse but that should not increase during expiration Finally the appearance *de novo* of such a murmur at the left lower sternal border in conjunction with the catastrophic preterminal cardiocirculatory events could also be consistent with perforation by the disease process of the interventricular septum with a left to right shunt however no thrill was described

What does the echocardiogram tell us? The echocardiographic dimensions are upper normal for both ventricles Hence this cannot be a very dilated heart There is posterior pericardial effusion in this echocardiogram Since the effusion does not appear anteriorly I would conclude that it is rather small and less likely to be causing cardiac compression The mitral valve echogram indicated prolapse with the anterior leaflet thrown posteriorly during systole (there is no tricuspid valve tracing) Ventricular wall movement looks poor with paradoxic septal motion This could be due to right ventricular volume overload but her pacemaker could have produced this since there is stimulation first of the right ventricle—the physiologic equivalent of delayed stimulation of the left ventricle In summary the echocardiogram only adds one fact to our knowledge i e that the cardiomegaly is partly due to pericardial effusion Left atrial size was normal in the echocardiogram yet there was a density on the chest film in keeping with left atrial enlargement

What do the lung scans tell us? Multiple pulmonary emboli are confirmed by lung scan In view of the peculiar constellation of clinical and laboratory findings the source of these pulmonary emboli becomes more interesting i e it could be the right heart or the systemic veins The patient had a very poor response to heparin with her partial thromboplastin time rising sharply This could also be explained on the basis of abnormal liver function She did not have disseminated intravascular coagulation

She developed spiking temperatures and this I assume was in the presence of multiple negative blood cultures The tuberculin test was negative The negative radiation physics studies rules out a leaky atomic pacemaker We are fairly certain that she did not have a protein losing enteropathy There was no evidence of bleeding to account for the dropping hemoglobin Terminally she spiked a very high white blood cell count (could the fever have been due to leukocytic pyrogen?)

Can we discern relationships among her long standing and more recent signs and symptoms? This is indeed a complex series of events each of which requires some explanation and an attempt to make sense of any patterns We must explain pre existing LBBB progressing to high grade A V block I am not aware of isolated congenital LBBB Though it may exist I think we consider virtually every case at any age to be acquired Here there is a very abnormal left ventricle as well as LBBB making this certainly an instance of intrinsic left ventricular disease Mitral prolapse by echocardiogram was present without a murmur or a click the ventricle was not severely enlarged Mitral regurgitation with ordinary congestive cardiomyopathy is nearly always associated with a disproportionately large left ventricular volume and left papillary muscle involvement can occur in infiltrative cardiomyopathy which is more likely to have a smaller ventricular volume Was the mitral prolapse a part of an unrelated click-murmur syndrome in which there is ventriculovalvular disporportion or is the prolapse due to acquired disease (cardiomyopathy involving or distorting the mitral supporting structures)? The possibility of artifactual echocardiographic prolapse must also be considered especially in the presence of pericardial effusion However this usually occurs with cardiac tamponade Finally tamponading pericardial effusion would have affected the heart sounds and might have caused the loss of any S_3 which was indeed absent despite several cardiac abnormalities The echo shows no evidence of a swinging heart and there was no pulsus para



Fig 3 Chest x ray *made on June 17 1974* First admission chest x ray shows mild to moderate globular cardiac enlargement minimal blood flow cephalization and a right ventricular pacemaker



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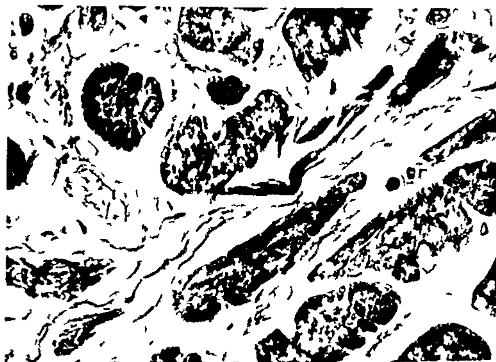


Fig 5 Interstitial fibrosis surrounding individual muscle fibers and interrupting their longitudinal course (Masson stain original magnification ×540)

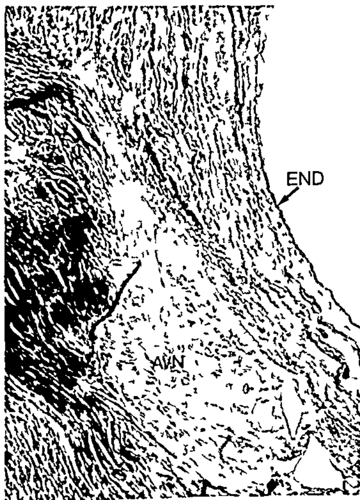


Fig 6 Terminal portion of A V node (left of center towards left lower corner) surrounded by dense fibrosis *AVN* = AV node *END* = endocardium (Masson elastic stain original magnification ×37)

doxus, more data against cardiac tamponade The main difficulty arising from the presence of pericardial effusion is the decision as to its origin i e, was it inflammatory or associated with congestive heart failure?

The terminal events including the spiking fever suggest blood stream invasion by pyrogenic material, however, all cultures were negative Despite this could this represent an infective endocarditis? It is particularly noteworthy that this occurred in the setting of preterminal pulmonary emboli Could a single catastrophe account for both blood stream invasion and pulmonary emboli? I shall return to this later

How to explain the progressive conduction system abnormality culminating in high grade A V block? Auto immune disease of the conduction system (Idiopathic Fibrosis) is frequent but usually occurs in much older patients This patient may have had an immunopathy touched off by a viral or other infection However the IgG would have risen and other proteins decreased so that this does not seem likely She lived in two countries in which echinococcosis is common and afflicts the heart, the pericardium and the liver In the absence of eosinophilia I think this is highly unlikely Could a connective tissue disorder account for the myocardial valvular, and conduction system lesions? This is entirely possible in a young woman Scleroderma heart

disease could equally be involved accounting for cardiac restriction the conduction abnormalities and the pericardial effusion Yet patients with scleroderma nearly always have prominent skin involvement and gastrointestinal problems and she did not Adult fibroelastosis and endomyocardial fibrosis seem unlikely in the absence of a prominent third heart sound

These significant rule outs leave us essentially with a disease of the walls of the heart i e a cardiomyopathy of some kind since there is no evidence of large or small vessel disease or of predominantly valvular or pericardial disease What valve malfunction there was could not explain the picture So this is a cardiomyopathy but probably not a primary disease of the heart muscle itself What kind of cardiomyopathy? Restrictive What kind of process causing restriction? This probably represents an infiltrative process a lesion that spreads in the myocardium and that tends to end in biventricular failure involving in the process the septum and conduction system and ultimately the mitral supporting structures What kind of infiltration? Possibilities include lymphoma sarcoid or a subacute infectious process Amyloid is another infiltration but this is a fairly young patient and patients with amyloid disease tend to be considerably older or have other chronic diseases You can have amyloid of the pericardium or the valves in unusual cases but her gum biopsy was negative and I would rule out amyloidosis There was no evidence for connective tissue disease or lymphoma Therefore this may be an inflammatory process i e a myocarditis What kind of inflammation? Given the tempo of progression of this syndrome a relatively slow granulomatous type of infiltrative process seems likely There are a number of these including the so called idiopathic giant cell myocarditis seen in young people with conduction abnormalities Tuberculous myocarditis must also be considered It is not common There are three forms—the large caseous type the miliary type (but this usually occurs in the presence of miliary spread) or a diffuse infiltration Diffuse tuberculous myocarditis advances slowly but ultimately involves the heart widely and also involves the conduction system You could construct a scenario that could account for the terminal events including the eventual loud murmur and the pulmonary infarctions One could hypothesize (or fantasize!) that the myocardial lesions ruptured the septum Now you could postulate that thrombotic material forming on the right side of the injured septum produced the pulmonary emboli With the hypothetical septal rupture infectious material could spread into the blood stream and a terminal miliary process could be seen in the liver and elsewhere This is one of the two possibilities The other possibility is sarcoid I would rather like sarcoid particularly in the absence of the murmur with a similar picture of AV block liver involvement and atrial arrhythmias as well as congestive failure The terminal events could be due to hemorrhage and central nervous system involvement But in sarcoid the IgG is elevated not down as in this case

With all the foregoing in mind it is time for conclusions We are dealing with a restrictive myocardiopathy which is secondary specifically infiltrative What kind of infiltration? Inflammatory What kind of inflammation? Granulomatous and probably with giant cells Therefore a chronic or subacute myocarditis My first choice is diffuse tuberculous myocarditis Second choice sarcoid Complications pulmonary emboli probably from the right heart

Dr Irwin K Kline The patient was a very slender and small woman about 4 ft 8 in in height The autopsy revealed a hypertrophied as well as dilated heart weighing 360 Gm containing mural thrombi both in the right and left ventricles The coronary arteries were patent throughout and a pacemaker electrode was impaled in the cavity of the right ventricular apex The endocardium of the left ventricle was moderately thickened and the left ventricular free wall was of increased thickness There was definite stiffness to the entire heart

The outstanding feature on microscopic examination was the presence of moderate to marked hypertrophic myofibers many of which were surrounded by slender strands of fibrous tissue and occasionally interrupting the course of individual muscle fibers (Fig 5) This is the picture most commonly seen with a post viral myocarditis In addition no parasites of the Chagas variety were noted Nor were there any stellate scars which would be indicative of the post Chagas type of cardiomyopathy These scars are readily apparent as noted in both experimental and clinical studies from South America

The conduction system was examined to corre



Fig 7 Interstitial myocarditis composed of lymphocytes with an occasional mast cell and some Anitschkow myocytes in edematous tissues (Hematoxylin and eosin original magnification ×540)

late the anatomic findings with the clinical irregularities Serial sections revealed that the A V node as well as the bundle of His were both surrounded and focally interrupted by chronic fibrosis (Fig 6) In addition, several areas of active myocarditis were noted where the interstitial tissue contained numerous round cells, primarily lymphocytes with occasional Anitschkow myocytes and mast cells (Fig 7) Several organizing microinfarctions were present in the high septum and fairly close to the conduction system These microinfarctions are most likely due to coronary emboli resulting from the left ventricular mural thrombus

Terminally there were multiple pulmonary emboli with pulmonary infarctions as well as renal infarctions These emboli had their origin in the right and left ventricles respectively The liver showed a typical congestive nutmeg pattern due to marked right ventricular failure The other organs showed no gross or microscopic abnormalities and examination of the brain was not permitted

In summary this was a case of a restrictive cardiomyopathy or a chronic active myocarditis of the so called pernicious variety which is most likely post viral in etiology Although viruses could not be cultured from this case, the microscopic appearance of the individual muscle fiber replacement and slender strands of fibrous tissue surrounding individual muscle fibers is highly suggestive of this type of process The foci of active myocarditis indicates the self perpetuating type of lesion that may be present in such cases These foci lead to exacerbations which is part of the clinical picture Unfortunately each exacerbation is worse than the preceding and the patients demonstrate a relentless downhill course Mural thrombi often contribute to the sudden ending as exemplified in this case

Final diagnosis Restrictive cardiomyopathy or chronic active myocarditis of the so called pernicious variety possibly post viral in etiology, congestive heart failure, AV block, multiple pulmonary emboli with pulmonary and renal infarctions

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The role of the central nervous system in chronic congestive heart failure

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Congestive heart failure, a very complex state, is the result of defective production and/or utilization of energy within the myocardium to provide mechanical pumping function. The metabolic and physico-chemical alterations within the myocardial cell of the failing heart initiate a wide variety of pathophysiologic responses which involve every organ of the body. These responses are so complex that it is virtually impossible to develop a unified comprehensive understanding of the mechanism and disturbances of congestive heart failure. That this is true is well illustrated by the fact that the members of the committee on heart failure at the Second National Conference on Cardiovascular Disease held in Washington, D.C., in November 1964 could not agree on a suitable definition of congestive heart failure. It is still not clear whether some of the disturbances in congestive heart failure are the cause or the result of the heart failure. These problems exist because of wide gaps in knowledge concerning the nature of the metabolic, physicochemical, and physiologic disturbances in congestive heart failure. Furthermore, there are qualitative as well as quantitative differences in the metabolic and physiologic defects associated with heart failure depending upon the etiology of the failure and the rapidity with which it develops.

In spite of the above difficulties in understanding congestive heart failure, no well trained clinician has difficulty in recognizing the signs and symptoms of congestive heart failure at the bedside. However, he certainly will have difficulty in understanding why a patient with valvular or coronary heart disease who had no previous history of breathlessness, liver enlargement, and pulmonary or central systemic venous congestion suddenly and often without apparent precipitating cause develops the signs and symptoms of congestive heart failure. A physiologist may explain the sudden change in the clinical state of the patient in terms of a right or left ventricular function curve relating (1) atrial pressure to stroke work, (2) ventricular end diastolic pressure to stroke work, or (3) change in myocardial fiber length to change in ventricular stroke work. Accordingly, as a ventricle fails, the ventricular function curve for that ventricle becomes lower and shifts to the right of the Starling curve so that eventually increments in filling pressure, ventricular end diastolic pressure, or diastolic fiber length either do not result in an increase in ventricular stroke work or may even result in a decrease in ventricular stroke work. But regardless of the value of the recorded cardiac output (high, low, or unchanged) the clinical syndrome of CHF clearly develops. As important as these observations may be to the understanding of congestive heart failure, they are merely mechanical descriptions of the failing heart. They offer no explanation as to why the heart has failed or why an increase in diastolic tension is associated with an increase in stroke work under certain circumstances but with a decrease in stroke work under other circumstances. Similarly, measurements of the concentration of intermediary metabolites in cardiac tissue or in coronary sinus blood may describe alterations in substrate utilization and metabolite production in congestive heart failure, but they provide no information concerning the mechanism of these alterations or the mechanisms responsible for the entire clinical syndrome of CHF.

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Fig 7 Interstitial myocarditis composed of lymphocytes with an occasional mast cell and some Anitschkow myocytes in edematous tissues (Hematoxylin and eosin original magnification ×540)

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constriction in CHF is evident to any astute clinician by the moist pale skin

Perhaps before and certainly when venous tone is increased renal sodium and water retention develops The retention of sodium and water seems to be the result of a dual mechanism First because of the inadequate cardiac output blood is shunted away from the kidneys so that the kidneys receive a smaller proportion of the cardiac output than during normal heart function—reflection of a compensatory action of the CNS and autonomic nervous system The decreased renal blood flow is therefore due to constriction of the afferent and efferent arterioles of the glomeruli Glomerular filtration rate (GRF) is reduced in absolute terms but is increased relative to renal blood flow (RBF) The filtration fraction (GRF/RBF) is increased because efferent arteriolar constriction is greater than afferent arteriolar constriction Thus just as the decrease in renal blood flow reflects sympathetic nervous system activity so the increase in the filtration fraction is a reflection of sympathetic nervous system activity which results in a disproportionate constriction of the afferent and efferent arterioles Under such circumstances proximal tubular reabsorption of sodium is increased and the quantity of sodium excreted in the urine is decreased [1]

The second mechanism responsible for the retention of sodium and water is related to the influence of adrenal hormones on the renal tubules Although the role of the adrenal hormones in the sodium and water retention of congestive heart failure is not completely understood it is possible to devise a working hypothesis as follows

Due to decreased pulsatile distension of the juxtaglomerular apparatus renin is released from the juxtaglomerular apparatus Renin in turn activates angiotensin from the alpha 2 globulin of the plasma and angiotensin stimulates the adrenal gland to secrete aldosterone The efferent stimulus for the secretion of aldosterone by the adrenal gland i e decreased pulsatile distension of the juxtaglomerular apparatus is mediated through the CNS and autonomic nervous system

Influence of the nervous system on venous tone

As already stated it is believed but not established that as cardiac output becomes inadequate relative to the needs of the body venous tone increases and systemic venous return and ventricular filling pressure increase resulting in an augmentation of cardiac output It is necessary at this point to define the term venous tone as well as to review the mechanisms by which venous tone is regulated by the nervous system [1]

Venous tone To use simple terms we shall consider basal or static venous smooth muscle tone functionally to be an expression of the basal or static tightness with which the wall of a vein fits around the column of blood within However the dimension size or caliber of the column of blood in a vein does not necessarily reflect the tone of the smooth muscle of the wall of the vein For that matter the tone of a venous segment which is engorged with blood may be high or low Furthermore in an open segment of vein the venous pressure may not necessarily reflect the level of the venous tone of that segment [1]

In more mechanical terms venous tone may be defined as the ability of a vein to resist deformation (strain) when subjected to a distorting force (stress) Deformation is usually considered as the percentage change in length of a material produced by a given stress (usually a weight suspended from the material) However for a blood vessel the percentage change in length is more conveniently considered as the percentage change in radius whereas the distorting force is expressed as a change in tension within the wall of the vessel The tension or tangential stress (T) within the venous wall is defined as

$$T = P(r/h) \qquad (1)$$

where P is the difference between the intravascular and extravascular pressures i e the distending pressure r is the radius of the lumen of the vessel and h is the thickness of the wall of the vessel Thus venous tone is mechanically determined by those factors contributing to the tightness or stiffness of the venous wall which determines the radius of the vein at a given tension The most important factors contributing to the stiffness or tightness of the vein may be expressed by the moduli of elasticity and viscosity of the venous wall and by the geometry of the wall (r/h)

It should be clear that tone and distensibility are different functions Distensibility (D) is defined by the relationship

$$D = (\Delta P/\Delta V)V \qquad (2)$$

where ΔP is the change in applied pressure ΔV is

It is probable that the fundamental subcellular disturbances which occur within the myocardium in congestive heart failure precede any measurable circulatory or hemodynamic alterations The methods for measuring such alterations are crude Thus the various hemodynamic disturbances which occur in congestive heart failure must be considered as late manifestations of congestive heart failure To a great extent the circulatory alterations in congestive heart failure appear to be compensatory However, in the later stages of failure these compensatory alterations overburden the heart so that a vicious cycle is instituted which if left uninterrupted, ends in the death of the entire organism

Many of the most important compensatory responses to congestive heart failure are mediated through the nervous system (the greatest integrater of organ functions in the body) particularly the autonomic nervous system The purpose of this report is to summarize some of the present knowledge regarding the role of the nervous system in congestive heart failure

Fundamental clinical alterations associated with chronic Congestive Heart Failure

Before describing the role of the nervous system in congestive heart failure it is advisable to review some of the fundamental alterations which occur in congestive heart failure

The heart responds to an increased load in at least one or more of four ways namely (1) hypertrophy, (2) increase in stroke volume (3) increase in heart rate, and (4) increase in rate of effort force or work (power) of myocardial contraction It should be noted that the nature of the load may vary among patients with CHF i e there may be a pressure overload (as with hypertension valvular stenosis) or a volume overload (as with anemia hyperthyroidism) Furthermore the load may be only relatively increased, i e, the demands upon the myocardium are normal but because of destruction of some myocardial tissue these normal demands must be met by a smaller number of contractile units which must work with greater effort

Depending upon the magnitude of the load its chronicity, and the state of the myocardium the compensatory adjustments may be adequate to meet the requirements of the tissues so that no clinical difficulties arise On the other hand a point may be reached at which cardiac output is no longer adequate to meet the needs of all the tissues The cardiac output at first is inadequate only upon exercise or stress but it may eventually also become inadequate even at rest At some time during the above chain of events the signs and symptoms of congestive heart failure develop The failure of the cardiac pump may, for a time, involve only one ventricle, i e the stroke output of one ventricle may exceed that of the other ventricle However, the output of one ventricle cannot exceed that of the other ventricle over a prolonged period of time[2] Whether the healthy ventricle actually fails in a given patient or merely readjusts its volume output to that of the diseased ventricle is a question which has not received adequate consideration but is beyond the scope of this discussion and involves measurements which are impossible to obtain accurately with existing methods It should be understood that in failure of the cardiac pump the cardiac output is considered to be inadequate to meet the needs of all the tissues important among which are probably certain crucial regulatory tissues such as the central nervous system (CNS) The cardiac output may be normal at rest, or in so called "high output failure," it may even be increased at rest Nevertheless an increase in cardiac output adequate to meet the requirements of all the tissues does not occur upon exercise or stress[3,4]

When the cardiac output becomes inadequate to meet the requirements of all the tissues a new system of priorities must be established i e, the circulation must be readjusted The proportions of the cardiac output going to the kidneys and skin are readjusted so that these organs receive relatively less blood than in the non failing state whereas the controlling mechanisms apparently give necessary preference to the CNS As will be indicated later in this discussion these readjustments are mediated largely through the central and autonomic nervous systems

When the heart fails there is peripheral vasoconstriction and a compensatory increase in venous tone which are associated with an increase in systemic venous return as well as an increase in right ventricular filling pressure For a while the increased filling pressure results in an augmentation of cardiac output This response is not necessarily evoked by an increase in the load or demand placed upon the heart but may develop as a result of an imbalance between demand and the cardiac output of a diseased heart working with greater effort The cutaneous vaso

and carotid sinuses Impulses arising in the aortic arch and carotid sinus receptors stimulate the inhibitory portion of the VMC which in turn inhibits the excitatory portion of the VMC so that sympathetic outflow is decreased

The interaction of the various reflex pathways concerned with cardiovascular regulation may be illustrated by the following example Let it be supposed that there is a sudden reduction in arterial blood pressure secondary to blood loss As arterial blood pressure in the aorta and carotid sinuses declines stimulation of the pressor receptors in these vessels decreases and in turn the number of impulses reaching the inhibitory portion of the VMC from the pressor receptors also decreases The inhibition of the excitatory portion of the VMC by the inhibitory center is diminished and sympathetic vasoconstrictor outflow increases The increase in sympathetic outflow results in increased arteriolar tone so that the peripheral vascular resistance increases In addition the capacitance vessels are constricted so that systemic venous return is increased (the volume of the peripheral venous reservoir is decreased) Finally the cardiac rate and the force and rate of myocardial contraction also are increased The net result of these responses is an increase in cardiac output or rate of work (power output) and arterial blood pressure to pre hemorrhagic levels In fact there may even be some degree of over shooting so that for a brief time arterial blood pressure is higher than before hemorrhage had occurred The blood pressure is adjusted downwards by reversing the process described above

There is some preliminary evidence that the influence of the sympathetic constrictor outflow may not be uniform throughout the cardiovascular system For example the frequency response curve to gradually increased vasoconstrictor stimulation is different for the resistance than for the capacitance vessels Thus for a given uniform sympathetic discharge constriction of the capacitance vessels may precede that of the resistance vessels Furthermore with the exception of the venules the veins are less influenced by local factors than are the precapillary vessels i e the resistance vessels where local myogenic and local humoral activity may predominate or at least greatly modify sympathetic constrictor stimulation whereas in the larger veins at least sympathetic vasoconstrictor control is dominant As will be indicated later the concept that sympathetic vasoconstrictor activity may be so integrated that some segments of the circulation are influenced relatively more than others may help to provide answers to some disturbing questions regarding the role of the nervous system in congestive heart failure

It should also be pointed out that the vasomotor center is influenced by impulses arising in the hypothalamus cerebral cortex and elsewhere in the central nervous system These central nervous impulses are responses to changes in function (physiochemical states) of the heart and circulation It is well known that emotional disturbances may produce reflex changes in vascular tone Although reflexes arising in the cerebral cortex may not independently play a role in the compensatory adjustments to congestive heart failure they certainly can modify these adjustments The importance of conditioned and orienting cardiovascular reflexes in congestive heart failure is unknown Again it is unlikely that conditioned and orienting reflexes play a major role in the pathogenesis of congestive heart failure in most patients However such reflexes may modify the compensatory adjustments to the failing heart in all patients and may even precipitate congestive heart failure in some patients The role of these and other reflexes in CHF certainly needs study

The role of the central nervous system in Congestive Heart Failure It is axiomatic that in chronic congestive heart failure the myocardium is diseased and dilated It is true that constrictive pericarditis may result in a clinical pattern which resembles congestive heart failure in the absence of significant myocardial disease Other exceptions also exist Nevertheless to focus on the rare occasions in which congestive heart failure exists in the absence of a cardiac lesion and a dilated heart would only detract from the fact that in the overwhelming majority of patients with chronic congestive heart failure the heart muscle is diseased and the heart is dilated acutely or chronically The heart disease in patients with congestive heart failure may be primarily disease of the heart itself or secondary to systemic disease

Associated with failure of the compensatory phenomena described above i e hypertrophy cardiac acceleration and increased force of

the volume change and V_0 is the initial volume of the vessel As already indicated the tone or stiffness of a vein is a function of the ratio of the radius of the vein to the wall thickness, i e,

Elastic stiffness = Tangential Stress = P (r/h) (3)

Because the large veins have a large radius as compared to wall thickness, they have relatively high moduli of elasticity Thus a large vein may be highly distensible but may actually be "stiffer" than an artery of comparable size

It would appear that the basal tone or stiffness of the veins is set at a certain level by some "catch mechanism" or "ratchet mechanism" located in the contractile fibrillae of the smooth muscle in the venous wall whereby venous tone at any given level is "set" or maintained for prolonged periods of time with low energy cost Any intervention mediated through the CNS and autonomic nervous system which lowers or raises venous pressure is associated with a change in venous smooth muscle tone which tends to restore the venous pressure to the level that existed at any other given time

Folkow[1] presented the interesting concept that because the precapillary resistance vessels subserve the local needs of the tissues these vessels possess a high degree of myogenic autoregulation On the other hand, the larger veins (capacitance vessels), because they subserve the needs of the entire organism through their influence on venous return and cardiac output are predominantly under central and autonomic nervous system control The intact veins of the human forearm display stress-relaxation and stress-relaxation recovery behavior[1] [1] These phenomena persist after anesthetic denervation of the vein Thus decreasing the volume and pressure in an isolated venous segment will result in an increase in the tone of the venous wall which will, within limits tend to restore the pressure in the segment to the initial levels Thus the veins are capable of some degree of autoregulation in that they "attempt" to maintain pressure at a certain level in the presence of disturbing physiologic influences However it should be understood that an increase or decrease in venous tone may occur with no change in the capacity of the venous reservoir Mobilization of blood from or into the venous reservoir can only occur when the veins constrict or dilate In this regard the veins as well as the peripheral blood vessels are strongly influenced by the CNS and autonomic nervous system

Role of the nervous system in myocardial contractility

Reflexes concerned with cardiovascular regulation The "vasomotor center" (VMC) is not a discrete anatomic entity but is rather a diffuse area of cells located in the dorsolateral reticular formation of the medulla oblongata and other parts of the CNS The vasomotor center may be divided into two functional parts namely an excitatory center and an inhibitory center Impulses from the excitatory center are distributed both to the heart and blood vessels via the sympathetic nervous system whereas impulses from the inhibitory center are distributed to the heart via the parasympathetic nerves but to the blood vessels via the sympathetic nervous system (e g, sympathetic vasodilator fibers) The excitatory and inhibitory portions of the vasomotor center are also mutually inhibitory

Vasomotor tone is regulated in part through the autonomic nervous system[1] [1] and its central connections The VMC maintains a certain level of resting basal nervous tone through the sympathetic outflow which maintains arterial blood pressure at about twice the level it would be in the complete absence of sympathetic outflow from the VMC On the other hand complete denervation of a vein does not produce a great decrease in venous pressure nevertheless venous smooth muscle tone is modified by the CNS and autonomic nervous system In general a decrease in sympathetic outflow results in a decrease in heart rate a decrease in the force of myocardial contraction, relaxation of arteriolar and venous tone and in turn a decrease in arterial and venous blood pressure On the other hand an increase in sympathetic outflow results in an increase in heart rate an increase in the force and rate of myocardial contraction, augmented arteriolar and venous tone and in turn an increase in arterial and venous blood pressure

The sympathetic outflow from the vasomotor center described above represents the efferent arc of the autonomic reflex pathways concerned with cardiovascular regulation Afferent impulses reach the VMC from affector sites scattered throughout the cardiovascular system important ones being the pressor receptors in the aortic arch

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myocardial contraction there is an increase in venous tone as well as in right atrial pressure. Thus, there is a rise in right ventricular filling pressure, and for each increment in filling pressure there is an increase in cardiac output. However, eventually a point is reached at which an increase in filling pressure is no longer associated with an increase in cardiac output and, indeed may be associated with a decrease in cardiac output. Thus an increase in venous tone at first contributes to compensation but later may possibly contribute to decompensation.[13] The increase in venous tone in chronic congestive heart failure is initiated and maintained by increased sympathetic outflow from the VMC. The evidence for increased venous tone in chronic congestive heart failure is:

1. Static pressure (mean circulatory pressure) is higher in patients with congestive heart failure than in patients without congestive heart failure.

2. Sympathetic ganglionic blockade produces a greater decrease in venous pressure in patients with congestive heart failure than in patients without congestive heart failure.

3. Digital rheoplethysmograms indicate that congestive heart failure is associated with marked increase in tone of the pre- and postcapillary blood vessels and that the postcapillary constriction tends to be greater than the precapillary constriction.

4. Exercise is associated with a much greater increase in venous pressure in patients with congestive heart failure than in normal patients.

The increased sympathetic discharge associated with chronic congestive heart failure is probably also responsible, at least in part, for increased salt and water retention associated with the congestive heart failure. It should be mentioned that it is claimed that the decreased ability of the kidney to handle a sodium load in chronic congestive heart failure may appear before an increase in venous pressure. However, as already mentioned, systemic venous pressure may not reflect regional venous tone. The question of whether sodium and water retention precedes the increases in venous tone is unanswered.

Hypothesis of neuropathophysiology of CHF

The clinical syndrome of congestive heart failure is to a large extent a functional disorder of the central nervous system and peripheral nervous system (α adrenergic and β adrenergic sympathetic nervous system). It is not primarily a disease of the central and sympathetic nervous systems but is secondary to a change in the function precipitated by the heart disease. The mechanism by which this generalized functional change in the nervous systems occurs is yet to be learned. The level of cardiac output itself does not trigger the central and sympathetic nervous system changes. The changes occur even when cardiac output at rest is no lower or even when it is higher than that of an individual sound asleep in bed at 3 o'clock in the morning. The cardiac, circulatory (systemic and pulmonary), renal, hepatic and cerebral pathophysiologic manifestations of CHF reflect the altered CNS and sympathetic nervous system function. The state of function of the nervous systems in CHF is not a disease state. This functional state is a state that any normally functioning CNS and sympathetic nervous system would develop in any person with heart disease that progresses to the stage of CHF.

Summary

Even though congestive heart failure is extremely common, the mechanisms responsible for the clinical manifestations remain a puzzle. The central and autonomic (sympathetic) nervous systems are responsible for a large part of the clinical manifestations. The role of the nervous system in CHF is discussed briefly. It is evident that there are many gaps in knowledge that remain concerning the role of the central, peripheral and autonomic nervous systems in congestive heart failure.

The peripheral vascular constriction, increase in venous tone and pressure, tachycardia, sweating, dermal pallor and tension and anxiety in patients with CHF reflect generalized sympathetic nervous system activity and the influence of the central and autonomic nervous systems on the clinical syndrome of CHF.

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constriction) Possibly in keeping with this proposal is the recent observation of Cambridge Davey and Massingham[7] who found that unlike phenoxybenzamine which blocks both pre and post synaptic alpha adrenergic receptors prazosin appeared to inhibit the post synaptic adrenergic receptor selectively in rabbit pulmonary artery Tritiated norepinephrine overflow during nerve stimulation a consequence of inhibition of the presynaptic adrenergic receptor[8] occurred following treatment with phenoxybenzamine but was not observed despite equally effective inhibition of artery contraction with prazosin

It is believed that the effects of alpha adrenergic receptor stimulation are mediated by a decrease in adenylate cyclase activity and cyclic AMP concentration in the post synaptic neurone Prazosin by virtue of its ability to inhibit phosphodiesterase activity might interfere with alpha adrenergic nerve function by preventing the fall in cyclic AMP which normally occurs following post synaptic alpha adrenergic receptor occupancy The biochemical steps which link occupancy of the pre synaptic adrenergic receptor to its biologic action inhibition of norepinephrine release have not been elucidated It seems reasonable to speculate that this effect might not be cyclic AMP mediated and might therefore be unaffected by prazosin

Experimental evidence suggests that the hypotensive effect of prazosin is not mediated through effects on the central nervous system or by inhibition of beta adrenergic receptors[2] Tachycardia and fall in blood pressure in response to isoproterenol are in fact enhanced by prior administration of prazosin in the rat

Systemic hemodynamic and renal responses to prazosin in man

Cardiac output is either increased or remains unchanged when blood pressure is lowered with prazosin in patients with essential hypertension Total peripheral resistance is significantly decreased In a small series of normal subjects and in patients with severe congestive heart failure prazosin was found to decrease both forearm vascular (arteriolar) resistance and forearm venous tone During passive head up tilt cardiac output falls and total peripheral resistance increases in hypertensive patients receiving prazosin although standing blood pressure is lower than supine blood pressure in patients receiving prazosin orthostatic hypotension is not commonly observed during chronic administration of prazosin[10] Renal blood flow (clearance of p aminohippurate) and glomerular filtration rate (inulin clearance or endogenous creatinine clearance) have been reported to be unchanged in patients receiving prazosin[10, 12]

Several observers have noted that the hypotensive response to prazosin is not associated with tachycardia[8, 10, 3] Plasma renin activity is not significantly increased in response to blood pressure lowering with prazosin[6, 0, 13, 16] Experimentally it has been observed that unlike hydralazine or diazoxide intravenous administration of prazosin failed to elicit an increase in plasma renin activity in the dog[17, 8]

The absence of tachycardia or increased renin release during prazosin administration contrasts sharply with changes in heart rate and plasma renin activity associated with administration of known vasodilator drugs such as hydralazine diazoxide nitroprusside and minoxidil Tachycardia and increased renin release observed when arterial pressure is decreased by arteriolar vasodilators are generally attributed to reflex sympathetic stimulation The failure to observe these sympathetically mediated responses during prazosin administration may be taken as evidence of the ability of prazosin to block sympathetic nerve stimulation As noted above the major effect of prazosin on adrenergic nerve function appears to be interference with alpha adrenergic stimulation the response of beta adrenergic receptors to the agonist isoproteronol was found to be enhanced by prazosin Since reflex tachycardia and increased renin release are mediated by beta adrenergic receptors the failure to observe these responses during blood pressure lowering with prazosin cannot be attributed simply to inhibition of alpha adrenergic nerve function Ganong found that alpha adrenergic blockade resulted in increased renin release in the dog Inhibition of central sympathetic discharge i e inhibition of both alpha and beta adrenergic function might provide a reasonable explanation for the absence of reflex increase in heart rate and renin release during prazosin administration but studies to date have failed to reveal evidence of a central site of action of prazosin Cambridge Davey, and Massingham[7] found that prazosin selectively inhibits post synaptic alpha adrenergic receptor function leaving presynaptic receptors intact It is conceivable that under conditions of selective post synaptic alpha adrenergic blockade norepi

Prazosin

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Prazosin (Minipress, Pfizer), 1 (4 amino 6, 7 di methoxy 2 quinazolinyl) 4 (2 furoyl) piperazine hydrochloride, was approved by the Food and Drug Administration for the treatment of hypertension in 1976 Structurally it combines the 4 amino pyrimidine moiety found in cyclic AMP and the dimethoxy benzo moiety of papaverine a recognized inhibitor of phosphodiesterase Studies in rat heart and aorta demonstrate that prazosin is a more potent inhibitor of cyclic AMP hydrolysis than is either theophylline or hydralazine[1] The drug is taken up rapidly by various tissues Its plasma half life is one to two hours but its hypotensive action is more prolonged presumably due to persistence of the drug at effective concentration at target sites It is excreted largely as a glucuronide metabolite in stool and urine[1]

Pharmacologic studies have suggested at least two different mechanisms responsible for the hypotensive effects of prazosin Constantine and associates reported that the intraarterial infusion of prazosin in the forelimb of the dog resulted in a dose dependent reduction in arteriolar resistance The effect on vascular resistance was markedly attenuated by pretreatment with the ganglion blocking agent hexamethonium, but was not completely abolished as was the vasodilation induced by the alpha adrenergic antagonist, phentolamine In contrast the vasodilatory action of diazoxide, a direct vasodilator, was unaffected by pretreatment with hexamethonium Constantine and colleagues[2] concluded that a significant component of the hypotensive action of prazosin was attributable to direct smooth muscle relaxation

While studies in the perfused forelimb suggest a direct vasodilator effect, studies in the intact animal indicate that the vasodilator effect is abolished by prior ganglionic blockade or alpha adrenergic blockade and make it appear more likely that the hypotensive action of prazosin is mediated predominantly by interference with alpha adrenergic stimulation of resistance vessels Graham and co workers[3] and Oates and colleagues[4] found that the hypotensive effect of prazosin was completely abolished by ganglionic blockade with pentolinium or alpha adrenergic blockade (phentolamine) in the anesthetized rat Scivoletto and associates found that the hypotensive effect of prazosin was abolished by alpha adrenergic blockade with ortho carboxy benzeno seleninic acid in the dog Further evidence that prazosin exerts a sympathetic blocking action comes from the observation that the decrease in vascular resistance in the limb of the rat perfused intraarterially with prazosin is dependent on the presence of intact sympathetic innervation of the limb[6] Further, prazosin causes epinephrine reversal [4] an action which is generally taken as evidence that a drug acts as an alpha adrenergic antagonist Finally prazosin decreases the pressor effects of infused norepinephrine[3,5] but does not block the pressor effect of angiotensin II[3] suggesting a specific interference with alpha adrenergic stimulation Unlike phentolamine which appears to function as a competitive inhibitor of norepinephrine at the alpha adrenergic receptor, prazosin does not protect alpha adrenergic receptors against irreversible inhibition by phenoxybenzamine This finding led Constantine and colleagues to suggest that prazosin in contrast to phentolamine does not act by competing for occupancy of alpha adrenergic receptor sites but rather by affecting some subsequent step in the sequence linking receptor occupancy to target tissue effect (vaso

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prazosin In many instances patients who experienced hypotension at the initiation of prazosin treatment tolerated further treatment with even greater doses subsequently

The occurrence of the first dose phenomenon in some patients does not appear to reflect greater plasma concentrations of prazosin[7] It has been suggested that the frequency of occurrence and the severity of the first dose phenomenon can be minimized by administration of a small dose initially and by taking the drug with meals rather than in the fasting state Dietary sodium restriction appears to predispose to the occurrence of severe initial orthostatic hypotension

In summary prazosin is an orally administered antihypertensive drug which appears to act as both a direct vasodilator and a sympathetic blocking agent It is unique among vasodilator drugs in that reflex tachycardia and increased renin release are not seen with blood pressure lowering It appears to be effective in mild moderate and severe hypertension As with most other antihypertensive drugs significant synergism with diuretics has been observed While orthostatic hypotension is not common acute hemodynamic collapse termed the first dose phenomenon has been observed in some patients at the onset of treatment with this drug but may be avoided if therapy is initiated with small doses

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nephrine release from presynaptic vesicles can be inhibited by the intact presynaptic receptors and thereby limit the 'overflow' of norepinephrine responsible for recruitment of closely associated beta adrenergic receptors during reflex sympathetic stimulation

Clinical application of prazosin

In double blind cross over or controlled studies, several groups[20, 21] have reported that prazosin 1 mg given three times daily was as effective as methyldopa 750 mg daily in lowering blood pressure of patients with mild to moderate hypertension

Bloom, Rosendorff and Kramer[21] compared prazosin and methyldopa in a double blind cross over study in 30 patients with mild and moderate hypertension The dosage of each drug was increased as needed to attain a standing diastolic pressure below 100 mm Hg A satisfactory blood pressure response was achieved in 16 of 25 trials with prazosin (mean daily dose 9 5 mg) and 17 of 27 trials with methyldopa (mean daily dose 1 325 mg) The incidence of side effects was comparable with the two drugs

In a multicenter double blind study Bradley and colleagues[20] found comparable blood pressure reduction in patients receiving prazosin (1 mg three times daily) and methyldopa (250 mg three times daily) When drugs dosage was increased to attain optimal blood pressure control, reduction of standing diastolic pressure below 100 mm Hg was observed in 14 of 19 (73 7 per cent) patients receiving prazosin (average dose 8 5 mg /day) as compared with nine of 19 patients receiving methyldopa (average dose 1 183 mg /day)

In a double blind cross over study comparing prazosin and hydralazine in patients receiving diuretics and/or beta blocking agents, Hua and associates[4] found that 1 mg of prazosin was roughly equivalent to 20 mg of hydralazine in potency but noted a significanly lower incidence of side effects requiring discontinuation of therapy with prazosin

The blood pressure response to prazosin was enhanced by concomitant administration of a thiazide diuretic in several controlled studies[22, 23] Cohen[2] found that the blood pressure response to the combination of prazosin with a thiazide diuretic (polythiazide) was significantly greater than that to either drug given alone Rougier and co workers[5] found that diastolic pressure fell below 100 mm Hg when thiazide diuretic was administered together with prazosin in 35 of 55 patients who had failed to respond to prazosin alone The synergist effect of prazosin and thiazide diuretics is generally most striking in patients with more severe hypertension or higher control diastolic blood pressure Although no controlled studies have yet been reported data presented by several groups[15, 1, 4] indicate further lowering of blood pressure when prazosin was added to antihypertensive regimens including propranolol, clonidine, methyldopa and hydralazine singly or in combination

Prazosin has been reported to be effective in lowering the blood pressure of patients with moderate and even advanced renal failure[1, 9] without adverse effect on residual renal function The observed decreases in forearm vascular resistance and venous tone[11] and the absence of tachycardia have led some investigators to suggest that prazosin might be effective in the treatment of intractable congestive heart failure by lowering preload and impedance[26]

Adverse effects

Side effects of prazosin include dizziness fatigue weakness, palpitations and headache In most reported instances these side effects have not been so severe as to require discontinuing the drug It appears that the occurrence of side effects of prazosin and their severity is less than that observed with methyldopa Laboratory abnormalities have been minor and inconsistent Positive Coomb's tests and drug induced lupus erythematosus have not been observed *

The most troublesome adverse effect of prazosin has been termed the first dose phenomenon In various reports from two to 16 per cent of patients given an initial dose of prazosin have developed severe orthostatic hypotension lightheadedness dizziness weakness or palpitations[7] These responses are almost invariably seen at the initiation of prazosin treatment and in most reported instances have followed the administration of 2 mg of the drug In one series[2] only two of seven patients who had experienced this first dose response when given 2 mg of prazosin experienced adverse effects, limited to mild dizziness when rechallenged with 0 5 mg of

*Lund-Johansen described one patient who developed a skin rash considered to be that of lupus erythematosus after 18 months of prazosin treatment Fever and joint pain occurred four weeks later following withdrawal of the drug The results of serologic studies (antinuclear antibodies, LE preparation) were not given

tuberculosis—none causes the valvular changes described in psittacosis Thus, if an infective agent provides the link between bird contact and valve disease it is probably *Chlamydia psittaci*

The concept of viral valvular disease suffers from a lack of evidence of past infection with cardiotropic viruses in patients with chronic valve lesions The fortuitous epidemiology of psittacosis provides indirect but suggestive evidence in the case of *Chlamydia psittaci* Consequently in one respect at least it is more suitable for study than for example the enteroviruses Further investigation is now indicated to clarify the relationship between *Chlamydia psittaci* and valvular heart disease This might take the form of

1 Follow up studies of proven cases of psittacosis
2 An investigation of the incidence of valvular disease in "at risk" groups of the population such as veterinary surgeons.
3 Studies of cardiac involvement in experimental models

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On the significance of an abnormal P-terminal force in Lead V_1

Left atrial enlargement produces a broad (0 12 second or greater) and bifid (interpeak interval > 0 04 second) P wave on the ECG A broad P wave may also be caused by an intraatrial conduction delay and hence this abnormality is not specific for left atrial enlargement An abnormal P terminal force in Lead V_1 (PTF V_1) is defined as a negative P in Lead V_1 the product of the depth (in mm) and the width (in second) of which is −0 04 mm second or less An abnormal PTF V_1 is a useful sign of left atrial hypertension e g in acute myocardial infarction. A recent echocardiographic study has shown that acute left atrial hypertension does not usually result in left atrial enlargement Conversely left atrial enlargement may occasionally be present without an increase in left atrial pressure Thus an abnormal PTF V_1 may be a sign of left atrial enlargement and/or left atrial hypertension When an abnormal PTF V_1 is seen in a patient with acute myocardial infarction the P wave often reverts to normal when the left atrial pressure returns to normal levels Thus this electrocardiographic sign is useful in following the course of patients with acute myocardial infarction

Severe right atrial hypertension may sometimes produce an abnormal PTF V_1 In this situation the physical examination and the ECG usually reveal evidence of right atrial enlargement (Tall P waves > 2 5 mm) and/or right ventricular hypertrophy A P vectorcardiogram will show a clockwise loop in right atrial enlargement with abnormal PTF V_1 whereas in

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"Rheumatic" heart disease, psittacosis and the importance of epidemiology

The evidence which supports the concept of viral valvular disease is fragmented several viruses are suspected of involvement but significant gaps exist in the chain of evidence which is quoted in support of an etiological connection The study of viral valvular disease may be facilitated if attention is focused first on identifying these gaps—and then on the systematic investigation of specific organisms which appear most likely to provide the missing answers

A connection between rheumatic fever and chronic valvular disease was substantiated by

1 Clinical evidence of valve lesions in patients with acute rheumatic fever

2 Postmortem demonstration of valve damage in patients dying from acute rheumatic fever

3 Follow up of patients recovered from acute rheumatic fever showing the development of chronic valve disease

4 Retrospective studies indicating that many patients with chronic valvular disease have a rheumatic history

When the evidence for virus valvular disease is assessed on this basis a major deficiency becomes apparent Evidence under paragraphs Nos 1 and 2 above has been established for several viruses and follow up studies comparable to those in paragraph No 3 are in progress However evidence under the fourth heading which is axiomatic if the proposed relationship is correct is more elusive It is difficult if not impossible to detect long past infection with most common viruses and yet the lack of such a link vis a vis viruses and valvular disease is a major weakness in the argument of those who propose that such a relationship exists Consequently any virus infection which not only causes acute valvular damage but for which there is also evidence suggesting its past occurrence in patients with chronic valve disease merits special attention One organism which goes some way towards fulfilling these criteria *Chlamydia psittaci* the causative agent of psittacosis has been largely ignored

Reports of valvular or endocardial damage in psittacosis

Descriptions of cardiac involvement in psittacosis are rare However in eight of 12 reports valvular or endocardial damage of one kind or another was noted Polayes and Lederer described postmortem findings in a 51 year old housewife who died from cardiorespiratory failure 11 days after hospitalization because of a cough and influenza Macroscopic and microscopic changes were present in the aortic mitral and tricuspid valves and included marked subendocardial deposits of fibrin in the middle aortic cusp Jannach described an 18-month-old child who died in congestive heart failure Numerous translucent glistening elevations 2 mm in diameter were present on the mitral valve cusps Discrete collections of lymphocytes and monocytes were found beneath the mitral valve endocardium The infiltration was prominent in the anterior papillary muscle and was associated with endothelial proliferation Dymock and colleagues[14] reported findings from a 13-year old boy who had rapidly progressive cardiac failure subendocardial accumulations of lymphocytes and monocytes were seen The findings described by Jannach[11] are particularly significant for they are reminiscent of the characteristic macroscopic appearances of acute rheumatic valvulitis Valvular damage due to *Chlamydia psittaci* in the form of infective endocarditis has also been reported The patients described by Scholte and by Grist and McLean[14] were probably examples of this entity Better documented cases have been published more recently [5-7] Diagnosis was based on histochemical staining, electron microscopy or immunofluorescent staining combined with serology Pre existing valve disease was not always present and in one case the illness was subclinical These reports are sparse but show that in most published cases of cardiac involvement in psittacosis the endocardium was affected

Epidemiological studies

Three epidemiological features of psittacosis are relevant to this discussion

1 Infection with *Chlamydia psittaci* is far more common than official figures suggest and often occurs as a mild febrile illness[18]

2 Most victims of overt psittacosis have a history of bird contact

3 Occupational contact with birds—by veterinary surgeons, pet shop owners or poultry workers—increases the risk of infection[8]

Many cases of psittacosis can be traced to pet birds and so it follows that as a group people who keep these pets have a greater chance of contracting psittacosis than people who do not Epidemiological studies have demonstrated a connection between bird contact and valvular heart disease[20] When patients with valvular disease were divided into those with and those without a rheumatic history it was found that a history of having kept pet birds was significantly more common in those who had not had rheumatic fever (63 per cent as opposed to 45 per cent $\chi^2 = 7.73$ $p < 0.01$) Furthermore using the same grouping of patients those with no rheumatic history more often developed symptoms of heart disease in the 15 years immediately following first contact with birds (46 per cent as opposed to 27 per cent $\chi^2 = 4.34$ $p < 0.05$) The findings relate to bird contact—not to psittacosis. However of the infections which have occasionally been acquired by man from birds[2]—St Louis encephalitis Japanese B encephalitis Murray Valley encephalitis West Nile fever Newcastle disease poliomyelitis salmonella and avian

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When the evidence for virus valvular disease is assessed on this basis a major deficiency becomes apparent Evidence under paragraphs Nos 1 and 2 above has been established for several viruses and follow up studies comparable to those in paragraph No 3 are in progress However evidence under the fourth heading which is axiomatic if the proposed relationship is correct is more elusive It is difficult if not impossible to detect long past infection with most common viruses and yet the lack of such a link vis a vis viruses and valvular disease is a major weakness in the argument of those who propose that such a relationship exists Consequently any virus infection which not only causes acute valvular damage but for which there is also evidence suggesting its past occurrence in patients with chronic valve disease merits special attention One organism which goes some way towards fulfilling these criteria *Chlamydia psittaci* the causative agent of psittacosis has been largely ignored

Reports of valvular or endocardial damage in psittacosis

Descriptions of cardiac involvement in psittacosis are rare However in eight of 12 reports valvular or endocardial damage of one kind or another was noted Polayes and Lederer described postmortem findings in a 51 year old housewife who died from cardiorespiratory failure 11 days after hospitalization because of a cough and influenza Macroscopic and microscopic changes were present in the aortic mitral and tricuspid valves and included marked subendocardial deposits of fibrin in the middle aortic cusp Jannach[1] described an 18-month old child who died in congestive heart failure Numerous translucent glistening elevations 2 mm in diameter were present on the mitral valve cusps Discrete collections of lymphocytes and monocytes were found beneath the mitral valve endocardium The infiltration was prominent in the anterior papillary muscle and was associated with endothelial proliferation Dymock and colleagues [8] reported findings from a 13 year old boy who had rapidly progressive cardiac failure subendocardial accumulations of lymphocytes and monocytes were seen The findings described by Jannach are particularly significant for they are reminiscent of the characteristic macroscopic appearances of acute rheumatic valvulitis Valvular damage due to *Chlamydia psittaci* in the form of infective endocarditis has also been reported The patients described by Schole and by Grist and McLean were probably examples of this entity Better documented cases have been published more recently Diagnosis was based on histochemical staining electron microscopy or immunofluorescent staining combined with serology Pre existing valve disease was not always present and in one case the illness was subclinical These reports are sparse but show that in most published cases of cardiac involvement in psittacosis the endocardium was affected

Epidemiological studies

Three epidemiological features of psittacosis are relevant to this discussion

1 Infection with *Chlamydia psittaci* is far more common than official figures suggest and often occurs as a mild febrile illness

2 Most victims of overt psittacosis have a history of bird contact

3 Occupational contact with birds—by veterinary surgeons pet shop owners or poultry workers—increases the risk of infection

Many cases of psittacosis can be traced to pet birds and so it follows that as a group people who keep these pets have a greater chance of contracting psittacosis than people who do not Epidemiological studies have demonstrated a connection between bird contact and valvular heart disease When patients with valvular disease were divided into those with and those without a rheumatic history it was found that a history of having kept pet birds was significantly more common in those who had not had rheumatic fever (63 per cent as opposed to 45 per cent χ = 7 73 $p < 0\ 01$) Further more using the same grouping of patients those with no rheumatic history more often developed symptoms of heart disease in the 15 years immediately following first contact with birds (46 per cent as opposed to 27 per cent χ = 4 34 $p < 0\ 05$) The findings relate to bird contact—not to psittacosis However of the infections which have occasionally been acquired by man from birds —St Louis encephalitis Japanese B encephalitis Murray Valley encephalitis West Nile fever Newcastle disease poliomyelitis salmonella and avian

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tuberculosis—none causes the valvular changes described in psittacosis Thus, if an infective agent provides the link between bird contact and valve disease it is probably *Chlamydia psittaci*

The concept of viral valvular disease suffers from a lack of evidence of past infection with cardiotropic viruses in patients with chronic valve lesions. The fortuitous epidemiology of psittacosis provides indirect but suggestive evidence in the case of *Chlamydia psittaci* Consequently in one respect at least it is more suitable for study than for example the enteroviruses. Further investigation is now indicated to clarify the relationship between *Chlamydia psittaci* and valvular heart disease This might take the form of

1 Follow up studies of proven cases of psittacosis

2 An investigation of the incidence of valvular disease in at risk groups of the population such as veterinary surgeons.

3 Studies of cardiac involvement in experimental models

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On the significance of an abnormal P-terminal force in Lead V_1

Left atrial enlargement produces a broad (0 12 second or greater) and bifid (interpeak interval > 0 04 second) P wave on the ECG A broad P wave may also be caused by an intraatrial conduction delay and hence this *abnormality* is not specific for left atrial enlargement An abnormal P terminal force in Lead V_1 (PTF V_1) is defined as a *negative P* in Lead V_1 the product of the depth (in mm.) and the width (in second.) of which is −0 04 mm second or less An abnormal PTF V_1 is a useful sign of left atrial hypertension e g in acute myocardial infarction A recent echocardiographic study has shown that acute left atrial hypertension does not usually result in left atrial enlargement Conversely left atrial enlargement may occasionally be present without an increase in left atrial pressure Thus an abnormal PTF V_1 may be a sign of left atrial enlargement and/or left atrial hypertension When an abnormal PTF V_1 is seen in a patient with acute myocardial infarction the P wave often reverts to normal when the left atrial pressure returns to normal levels Thus this electrocardiographic sign is useful in following the course of patients with acute myocardial infarction

Severe right atrial hypertension may sometimes *produce an* abnormal PTF V_1 In this situation the physical examination and the ECG usually reveal evidence of right atrial enlargement (Tall P waves > 2.5 mm.) and/or right ventricular hypertrophy A P vectorcardio*gram will show* a clockwise loop in right atrial enlargement with abnormal PTF V_1 whereas in

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left atrial enlargement the loop is counterclockwise An echocardiogram will also be of value in the differential diagnosis of an abnormal PTF V_1 caused by left atrial enlargement as opposed to that due to right atrial enlargement The ratio of the left atrial diameter to the root diameter is > 1 2 in left atrial enlargement In summary an abnormal PTF V may be caused by (1) left atrial enlargement (2) acute left atrial hypertension without enlargement and (3) severe right atrial hypertension The differential diagnosis of these conditions may be further elucidated by vectorcardiography and echocardiography A more specific interpretation of the commonly used term left atrial abnormality may therefore be possible

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Analgesic abuse and microvascular changes

The toxic effects of drugs on the kidney have been the subject of much research In some instances the damage that occurs is clearly the result of hypersensitivity reactions but with many other drugs the exact mechanism responsible for the observed effects has not been elucidated That analgesic abuse can cause renal papillary necrosis and cortical interstitial fibrosis has been well documented but the manner in which the renal papilla undergoes necrosis has largely eluded research workers The recent observation of marked thickening occurring in the walls of small submucosal vessels of the renal tract in patients with analgesic nephropathy adds a new dimension to the possible pathogenesis of analgesic induced papillary necrosis The microvascular changes described extend from the renal papilla to the submucosal vessels of the pelvis ureter and bladder It is suggested that it is this thickening of the walls and resultant narrowing of the lumen in vessels of the renal papilla and pelvis that is responsible for the infarct like necrosis of the papilla that occurs in the presence of analgesic abuse [1] In those patients in whom the microvascular abnormality has been observed the excessive analgesic intake was either phenacetin or paracetamol containing compounds Recent studies in patients with analgesic nephropathy have revealed that following the ingestion of phenacetin or paracetamol by these patients a greater than normal proportion of the drugs and their metabolites appear in the urine in a non conjugated form It is not known whether this is an expression of a functional defect of hepatic microsomal enzymes or due to lysosomal or bacterial deconjugating enzyme action within the urinary tract Both are possible mechanisms and it is worth noting in this regard that patients with analgesic nephropathy have an excessive deposition of lipofuscin pigment in the liver and associated organelle damage as seen on ultrastructural examination [2] The non conjugated form of the excreted drug is more lipid soluble and tends to diffuse back across the urinary epithelium through the submucosal tissue where it may have a deleterious effect upon the vascular tree The vascular changes are seen to be most marked at those sites where one expects the drug to be present in high concentration namely the renal papilla and along the pathway of the urinary stream in the pelvis ureter and bladder In the latter site the changes are found mainly in the submucosal vessels where the ureter enters the bladder and to a much lesser extent in vessels away from this area It is interesting to speculate as to whether the changes in the vessels are confined to the renal tract or whether the non conjugated drug which tends to persist in the body has similar toxic effects elsewhere in the organism Preliminary observations suggest that some narrowing of dermal vessels may also occur in patients with analgesic nephropathy

In summary we are of the opinion that the presence of these vascular changes in the renal tract and possibly the dermis in patients who abuse analgesics will open new vistas in the study of the toxic effects of drugs

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Of the mind of man

The greatest natural resource of any nation is the mind of man The mind is most important in any endeavor of man regardless of its nature And this is true in cardiology The advancement in the field of cardiology from practically nothing of note in the dark ages of civilization to the developments and knowledge that exist today is remarkable The greatest therapeutic advancement for the benefit of the sick was the discovery of penicillin This antibiotic and many others which followed eliminated syphilitic heart disease and arterial aneurysms eliminated death from bacterial endocarditis made intricate cardiac surgery possible and helped to control and cure complicating and associated infections in cardiac diseases etc Better nutrition public health improved housing clothing and other changes reflect the fruits of the minds of people By supporting thinkers scholars researchers and teachers so that they can be free from the burdens and rules of accountability and the practices and pressures of popular research teaching and politics man can tread into the future with confidence and continue the advancement of cardiology and medicine Truth will prevail and false claims succumb with time Man with his active fertile mind will assure the survival of man and the advancement of health and improvements in cardiology *There is no need for example to* fear critical shortage of energy Let the mind of man be free and be encouraged to venture in thought and research and the energy shortage will be solved and all people will profit Cardiology has a great future through the mind of man To cardiologists 100 years hence the cardiology of today will appear archaic This is to be expected because of the mind of man, the greatest resource of any nation Nurture it support it unburden it and keep it free

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Letters to the Editor

Differences in Coronary Care Units

To the Editor

In a recent annotation (AM HEART J 91 673 1976) Lindholm and colleagues[1] challenged the value and effectiveness of coronary care While their views certainly are shared by some they would be rejected by the majority of cardiologists in this country Perhaps the differences in attitude relate to what one calls a Coronary Care Unit Australian coronary care units have followed the general pattern of the original unit established by Julian[2] at Sydney Hospital with patients having suspected or proven infarction being monitored in as peaceful an atmosphere as possible by nursing staff trained in intensive coronary care The coronary care unit in Dr Lindholm s hospital as described elsewhere comprises beds with E C G monitoring facilities in a busy general medical emergency admission department

In this country the hospital mortality rate for patients with definite infarction who progress through coronary care wards of major hospitals is around 16 per cent and we hopefully look to further reduction of this figure with implementation of measures to reduce infarct size If our hospital mortality figures were as high as those published by Dr Lindholm and colleagues—41 per cent for all patients 33 per cent for those 69 and under we would probably share his views The published figures however suggest that Dr Lindholm and colleagues should look within their hospital for an answer before projecting their views to other hospitals with completely different arrangements (and results)

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Differential refractoriness of ventricular specialized conduction system

To the Editor

We have read with great interest the paper by Cannom Goldreyer and Damato entitled A demonstration of differential refractoriness within a single fascicle of the human ventricular specialized conduction system which appeared in the June 1975 issue of the Journal (AM HEART J 89 ... 1975) The authors are the first to demonstrate with clinical electrophysiological methods that two areas of different refractoriness may exist within the right bundle branch (RBB) of which the more distally located area is more refractory They are the first to show an A V gap phenomenon due to decreased conduction velocity in a proximal region of the RBB We would like to make a comment concerning the maximal refractoriness within the RBB The authors suggest that the effective refractory period (ERP) located relatively distal within the RBB represents the area of maximal refractoriness Every premature supraventricular impulse which blocks below the His bundle does so at a gate or site of maximal refractoriness A zone of maximal refractoriness was initially encountered within the RBB when the premature impulse first blocked below the His bundle" We are not in agreement with this opinion

Due to the limits of the indirect methods of clinical electrophysiology in the intact human heart regions with longer ERPs in an electrophysiologically heterogenous RBB can not be demonstrated if functional refractory periods (FRPs) of more proximal regions exceed the ERPs of the adjacent distal portions Thus it is obvious that in the case demonstrated by the authors it can t be proved that the relatively distally located region with the longer ERP represents the region of *maximal* refractoriness Within an even more distal area of a depressed RBB regions with longer ERPs may exist Obviously the initial refractoriness may represent the maximal refractoriness but this possibility can't be verified by the indirect technics recently employed in clinical electrophysiology We think that the title of the excellent paper reflects exactly our opinion concerning refractoriness the authors demonstrate differential refractoriness within a single fascicle of the human ventricular specialized conduction system and nothing more

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Arterial thromboembolic complications with aortic ball valve prostheses

To the Editor

In a review paper on arterial thromboembolic complications in patients with a Starr Edwards aortic ball valve prosthesis Dale[1] concludes that arterial thromboembolic complications represent a major threat to patients even several years after the operation *in spite of intense anticoagulant therapy* Th

conclusion implies a major shortcoming of such therapy Fortunately however the author defines his aim and achievement with respect to the intensity of oral anticoagulation The aim was 5 to 15 per cent Thrombotest only slightly more than one third of the patient values were ≂ 10 per cent in terms of Thrombotest

The reader unfamiliar with oral anticoagulation controlled by Thrombotest is likely to accept the author s opinion that anticoagulation intensity in this range is adequate particularly because such Thrombotest values have long been and are still propagated as therapeutically optimal values in arterial thrombosis. On the Continent the Scandinavian protagonist of Thrombotest proposed at the introduction of Thrombotest in 1959 an optimal therapeutic range of 10 to 30 per cent However this range has been applied without success in patients with the cloth-covered Starr Edwards prosthesis No 2300 aortic and No 6300 mitral In spite of this failure a target value of 15 ± 5 per cent is still haunting the literature in 19 6 That anticoagulation with a hi h proportion of the Thrombotest values lying ≥ 10 per cent is unlikely to be succes ful can further be concluded from the results of many well designed clinical trials.

In The Netherlands where Thrombotest has been used since 196? by an increasing number of laboratories responsible for laboratory control of outpatient oral anticoagulant treatment (at present more than 50 000 patients including a large number with a heart valve prosthesis) the therapeutically optimal range is 5 to 10 per cent with a target value range of 7 to 8 per cent In three double blind trials on long term anticoagulation treatment performed in The Netherlands between 1965 and 1968 the values of 5 to 80 per cent of the patients lay below ≂ 10 per cent Thrombotest At present with computer assi ted regulation of the dosage of the anticoagulant, outpatients can easily be maintained at a level of ≂ 10 per cent for 80 to 85 per cent of the time

Patients with a heart valve prosthesis should receive particularly tight and even more intensive treatment the optimal range in terms of Thrombotest being 4.5 to 8 per cent with a target value range of 6 to 7 per cent With this regimen we very seldom see thromboembolic complications in artificial heart valve patients, which is consistent with the results obtained in the well controlled study of a Canadian author

It should be realized in this context that it is not only Dutch experience which has shown that Thrombotest takes an exceptional position American and British experts in the field came to similar conclusions as early as 196? That the Dutch intensity of treatment is not exaggerated is also evidenced by the risk of bleeding complications, which proves to be acceptable It is clear however that the inten ity of treatment as applied in The Netherlands is not exceptional as such, but only with respect to the terms of percentage coagulation activity according to the producers *standard ref rence curve* In those terms it is much lower indeed than in t rms of the conventional percentages according to Quick ol tained with any of the other thrombopla tins used for anticoagulant control

It is to be hoped that the report of the international prothrombin time standardization trial performed under the joint aegis of the International Committee on Standardization in Haematol gy (ICSH) and the *International* Committee on Thrombosis and Haemostasis (ICTH) will be used as a guide to national anticoagulant control panels for standardization of the prothrombin time and by this to a better definition of the proper therapeutic range to be aimed at with the many different types of thromboplastin and methods of control Once this has been achieved disappointing observations such as those reported by Dale should no longer occur

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Reply

To the Editor

Dr Loeliger and associates criticize the intensity of the anticoagulant treatment reported in my paper[1] where the therapeutic range was considered to be from 5 to 15 per cent of normal coagulation activity as measured by Thrombotest (TT)[2] I agree that the therapy is optimal when the TT is kept between 5 and 10 per cent and this level is now propagated by the producer and is the accepted one in our country

The slightly higher values had however been allowed mainly for two reasons Firstly because the hazard of strict anticoagulation in such patients is severe bleeding and fatal intracranial or other types of hemorrhage are not rare[3] Two patients in my study died from bleeding that occurred on TT values of 5 and 11 per cent Patients with prosthetic ball valves might be particularly susceptible to hemorrhage because they have a considerably reduced platelet adhesiveness and a prolonged bleeding time The recommendation by Dr Loeliger and associates that valve patients should have particularly intensive anticoagulation could therefore have serious consequences and I fear that an increased number of bleeding episodes would more than counterbalance a possibly better effect on thrombus formation

Secondly slightly higher values were used because of the practical difficulties connected with control of anticoagulant therapy in patients living in all parts of Norway often very far from the control laboratories Nevertheless the intensity of anticoagulation was consistently satisfactory in approximately half of the patients even after the standards outlined by Dr Loeliger and associates and higher levels are accepted by several centers Furthermore I have later collected information of all TT values throughout the period since the distribution of the values reported in the paper reflected only the levels at follow up This demonstrated that 86 per cent of the values fell between 5 and 15 and 55 per cent fell between 5 and 10 per cent of normal activity To my knowledge a more consistently intensive anticoagulant therapy in materials concerning patients with prosthetic valves has not been presented

The relation between the intensity of the therapy and the incidence of arterial thromboembolic complications has been evaluated further The rate of thromboembolism was however not lower in the patients with the majority of their TT values at 10 per cent or lower than in the others This supports my conclusion that such complications represent a major threat to the patients in spite of intensive anticoagulant treatment

Dr Loeliger and associates seek support for their assertion that intensive anticoagulation can effectively prevent arterial thromboembolism in patients with prosthetic heart valves from a Canadian study This is surprising since they stress the importance of prothrombin time standardization because in that paper not even the type of thromboplastin used is mentioned A direct comparison is therefore not possible but it is not improbable that the majority of my patients received what was considered satisfactory anticoagulation in that study Furthermore only 33 patients received what was defined as adequate therapy and one had a thromboembolic complication Moreover most patients had mitral or tricuspid valve replacement which would predispose for thrombi of a more venous composition That this type of thrombosis can be effectively prevented by anticoagulants is well established

It is astonishing that Dr Loeliger and associates build the assertion on this study alone since only 13 of the patients with single aortic valves had received adequate anticoagulation

Dr Loeliger and associates state that they very seldom see thromboembolic complications in patients with artificial heart valves A better documentation of the intensity of the treatment its antithrombotic effect and the rate of bleeding complications would however be more valid

Finally their assumption does not take into consideration the role of the platelets for the thrombotic process While the dominant mechanism for venous thrombosis is plasma coagulation platelet aggregation is important for the formation of arterial thrombi Although adequate anticoagulation certainly is of some benefit it does not affect the reactivity of the platelets Therefore arterial thrombosis on prosthetic aortic valves will most probably represent a problem even during very intensive anticoagulant therapy

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More on high school health curricula

To the Editor

I was relieved to discover that the problem of an inadequate and inappropriate high school health curricula was at last cited by Dr Mroczek in the AMERICAN HEART JOURNAL I would like to add three points to his editorial

My first point is to label high school health textbook material as also being inadequate and inappropriate If you will observe the contents of most high school (and some college) health texts you will discover an imbalance in subject matter favoring subjects other than cardiovascular disease and cancer The one thing that I can remember from my high school health education is the proper *procedure for* brushing *my* teeth Cardiovascular disease was not even mentioned in high school curriculum at this time (early 1960s) I believe high school health care texts should be joint authored by the physician exercise physiologist and health educator alike

My second point is more specific to my own profession High school physical education classes are often an unstructured and non-educational experience Inappropriate curricula is the culprit here as well Overemphasis on superior athletic performance body physiqu and non dynamic forms of exercise have been the rule rather than the exception Cardiovascular endurance types of exercises and recreation should be *at least* 60 per cent of the emphasis If secondary school curriculum specialists would just wake up and start reading even a portion of current medical literature relating to exercise physiology the problem would be partially solved

Finally my last point is what I believe to be the crux of the problem The training of health educators at the college level is far out of li e Speaking from my own experiences some of the nation s largest and supposedly most prestigious universities are the most misaligned with regard to the training of secondary school health educators Regardless of how well we improve college level health education textbooks we still see the type of professor who remains bolted to a few 40-year-old ideas I m speaking specifically about neglecting to teach life long cardiovascular endurance exercise habits and how they frequently have a positive effect on CHD related risk factors Nearly every significant piece of research that has been published in the last 6 years has been either ignored or is contrary to what is presently taught in many high school physical education classes There is no excuse for ignorance regarding the proper forms of exercise when you consider the availability of current publications

My suggestion is that we re-educate some of the professors who are responsible for instilling (or not instilling) health care information into our secondary health education teachers One step further—evaluate the chairmen of university health, physical education, and recreation departments.

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Nitroglycerin ointment therapy and leg edema

To the Editor

Topically applied nitroglycerin ointment has been well demonstrated to have a sustained vasodilatory effect and therefore its use has become fairly commonplace in the chronic therapy of angina pectoris and congestive heart failure

It has also been d mon trated that the major vasodilatory action of nitroglycerin is on th venous circulation resulting in a reduction in venous return and left v ntricular filling pressure (preload)

I have recently ob erved two cases in which the onset of gross lower extremity edema followed within one week the institution of nitroglycerin ointment therapy

The first case is that of a ?7 year old man who because of chronic severe angina was placed on 2 per cent nitroglycerin ointment 1 inch application every 4 hours one week prior to admission for coronary angiography Beginning about five days prior to admission this man who had never had any previous symptoms of congestive heart failure began *to note* the onset of pedal edema for the first time By the time of admission his house physicians noted new 3+ edema of his right leg the source of a saphenous vein for *earlier coronary* artery bypass grafting and 1 2+ edema *of his left leg* and initially felt that he had developed congestive failure Closer examination, however revealed no other evidence of right or left heart failure The edema resolved easily with *diuretic* therapy Later therapy with nitroglycerin ointment 1 ? *inches* application every 4 hours plus hydrochlorothiazide ?0 mg by mouth every day resulted in no further edema

The second case is that of a ?6-*year old man* with chronic biventricular failure secondary to diffuse *coronary* disease with diffuse left ventricular hypokinesis mitral regurgitation and an elevated left ventricular end-diastolic pressure of ?? demonstrated by catheterization in 19 ? Since that catheterization he has had several admissions *for control of* his congestive heart failure the last being in February 197? at which time mea *urements* via a balloon tipped thermistor catheter revealed a cardiac index (C I) of 1 4 and pressures as follows right ventricle 60/23 pulmonary artery 60/34 and mean pulmonary capillary wedge ($\overline{PCW}$) 33 mm Hg He was initially treated with small doses of intravenous nitroprusside (0 μg /Kg /hr) which resulted within 24 hours in a marked improvement in dy pnea associated with an improvement in his C I to 2.3 and $\overline{PCW}$ to 16 He was then switched to non parenteral therapy and was *eventually* discharged on digoxin 0 1?? furosemide 1?0 mg twice a day hydralazine 30 mg four

times a day KCl 20 mEq twice a day and 2 per cent nitroglycerin ointment 1 inch every 6 hours

One week after discharge he presented with a 5 8 kilogram weight gain over his lowest hospital weight and painful 4+ peripheral edema though experiencing continued relief of dyspnea his previous limiting symptom and continued roentgenographic clearing of the lung fields Despite discontinuation of his nitroglycerin therapy elevation of his legs and more diuretic therapy his edema has been very difficult to resolve

The temporal relationship of the onset of peripheral edema (or sudden worsening thereof) in these two patients to the institution of nitroglycerin ointment therapy suggests a link between the two The likely sequence of events in the genesis of the edema is that nitroglycerin ointment causes sustained venodilatation which leads to venous pooling which eventually results in high peripheral venous hydrostatic pressure which of course results in transudation of fluid In the first case this sequence was probably aided by previous stripping of the right superficial saphenous vein In the second case the sequence was probably aided by persistent poor pump function and also perhaps by hydralazine therapy which by lowering arterial resistance would allow ready forward access of fluid to the capacitance vessels

These two cases represent good clinical demonstrations that nitroglycerin ointment does have a sustained hemodynamic effect and that its venodilatory effect is a strong one The onset of new or worsening peripheral edema soon after the institution of nitroglycerin ointment therapy should be watched for and recognized as a possible side effect of that therapy especially in patients with predisposing conditions such as poor left ventricular pump function and pre existing venous insufficiency

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References—dog s tails?

To the Editor

Who would submit a medical article for publication with a comprehensive appendage of references dating back if possible to Gutenberg? At present authors seem to think that references adorn an article and the greater their number the more they bespeak the diligence of the authors, their knowledge of the literature their erudition and the accessibility of a well stocked library The number of references in the average article makes one think that the tail is wagging the dog

This is a plea not only to save paper and ink and the time of editors and reviewers but to limit references to the one or two most recent articles on a subject indicating that all that has been written in the past will be found in them For example

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Chromosome aberration in ectopia cordis (46 XX 17q+)

To the Editor

Thoracic ectopia cordis is a rare congenital malformation which usually results in death soon after birth Although many reports exist on management of patients with various types of ectopia cordis very little information is available regarding its etiology Specifically the paucity of data on chromosome studies in these patients is striking Following is a brief description of a patient with ectopia cordis in which chromosome studies showed additional chromosome material attached to the long arm of chromosome 17

Case report

Patient B H a 2 550 gram Caucasian female infant was born at 36 weeks gestational age Multiple congenital anomalies including thoracic ectopia cordis cleft lip and palate and hydrocephalus were noted at birth The infant died at 9 hours of age Additional autopsy findings were tetralogy of Fallot with extreme dextroposition of the aorta anomalous origin of the left coronary artery bi lobed right lung and occipital meningocele The pregnancy was complicated by a septate uterus and pre-eclampsia Medications ingested during the first 3 months of pregnancy included Combid spansule capsules and Bendectin tablets Fetal bradycardia of 40/minute was noted during labor The mother was a 21 year-old primagravida The father was 26 years old Both parents were in good health and their respective family histories were negative for birth defects. Consanguinity was denied Chromosome analysis using peripheral blood from the infant showed

extra material on chromosome 17 (46,XX 17q+) The origin of this material could not be established Cytogenetic studies of the parents showed no abnormalities.

The discovery of a chromosome abnormality in this patient with ectopia cordis is to the best of our knowledge the first reported such case It may be that this is an entirely coincidental finding since a patient with thoracic-abdominal ectopia cordis and normal chromosomes has been reported Nevertheless, it appears that further cytogenetic studies on these patients utilizing advanced techniques are necessary before the possibility of a chromosome aberration can be eliminated The drugs ingested by the mother during pregnancy may also be considered teratogenic but we are not aware of any report indicating such a relationship at present

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Excitation–contraction abnormalities and heart block

To the Editor

We have read with great interest Dr Burch s short article on the time course of contraction of the myocardium and its effect upon myocardial function in a recent issue of the JOURNAL.

It is reasonable to suppose that excitation–contraction relationships in the heart are very important and that abnormalities in the time course of contraction may be responsible for intraventricular bundle branch block Dr Burch mentions RBBB LBBB and arborization block or defective intraventricular conduction but fails to discuss the WPW blocks (LV RV septal types) and the pre-excitation syndrome These are very real problems in cardiology

Is it not reasonable to suppose that some contraction abnormalities, even more complicated than those that occur in RBBB LBBB and arborization block are responsible for Wolff Parkinson White blocks in patients? This point is certainly a very important one

Dr Burch is doubtless aware of the work of Lenègre on the bundle branch blocks the latter s investigations have indicated that most cases of intraventricular block have intraventricular cavity dilatations. Is it not possible to presume that excitation–contraction abnormalities in patients with defective intraventricular conduction systems may be one of the causes of ventricular dilatation and failure in the Wolff Parkinson White syndrome as well as in the others

Dr Burch s article gives us an excellent explanation of different disturbances in the order of electrical activation of the myocardium on conduction system defects but we would like to see if possible a more detailed study on each separate manifestation of bundle branch blocks.

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Aortic valve prostheses rheumatic fever and lone aortic regurgitation

To the Editor

I have recently commented on the late development of mitral stenosis in patients who have had mild to moderate mitral regurgitation following their initial attack of acute rheumatic fever An interesting observation in patients who have undergone aortic valve replacement eight to twelve years ago for apparent isolated aortic regurgitation deserves comment. These patients were young patients and were known to have had rheumatic fever With continued follow up it has become apparent that some will develop mitral valve disease years later[2] Quite obviously although aortic valve replacement changes the natural history of that valve it does not change the pattern of mitral valve disease In the last six months two patients have been found to have developed mitral stenosis and the insufficiency of mitral valve deformity In both patients this diagnosis was suspected by the appearance of a diastolic rumble and a faint opening snap The appearance of a new systolic murmur at the apex radiating to the axilla has clinically been a difficult auscultatory phenonema to evaluate in patients with Starr Edwards prostheses because of the wide radiation of the systolic flow murmur of this particular valve Careful repeated evaluations by the same observer may give a clue by the change in the character of the systolic murmur with passing years In both patients an echocardiogram supported the diagnosis of mitral valve disease and in one cardiac catheterization was also confirmatory Both patients presented with increasing cardiac symptomatology increasing shortness of breath, palpitation and fatigue

Two specific points must be made Firstly worsening of cardiac symptoms in a patient with an aortic valve prosthesis need not be related to prosthetic valve malfunction or myocardial disease but may obviously be related to the late development of mitral valve disease The clinical diagnosis of this may be partially obscured by the auscultatory findings associated with the prosthetic valve Echocardiograms are invaluable in further evaluation Secondly lone aortic regurgitation in young people is frequently rheumatic in origin As we have shown previously aortic regurgitation is the more persistent of the two lesions of acute rheumatic fever (aortic regurgitation and mitral regurgitation) It is the new appearance of lone aortic regurgitation in the older group that should raise the question of an etiology other than rheumatic fever

Lone aortic regurgitation in young patients may ultimately become combined aortic and mitral disease of the older patient with rheumatic heart disease

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The Pathology and Surgery of the Veins of the Lower Limb 2nd Ed Edited by Harold Dodd and Frank B Cockett New York 19 6 Churchill Livingstone 323 pages Price $39 50

The second edition of *The Pathology and Surgery of the Veins of the Lower Limb* edited by Dodd and Cockett is an excellent book on a common and too frequently mismanaged disease There are six contributors to the book The di cus sions of anatomy pathology and physiology are clinically oriented to make it easier for the surgeon and other physicians to manage better venous diseases of the legs The book consists of three parts Part I is concerning with history anatomy and physiology Part II with pathology and surgery of the deep and communicating veins The book is excellent and certainly a source of information essential for those who treat venous diseases of the legs, whether or not it is surgical or medical management The illustrations are excellent The reviewer is impressed with the poor application of a bandaging in general use Figs 183 and 184 on pages 2?? and 273 illustrate a *smooth application* but this u ually remains smooth for a few minutes to a few hours and the patient finally finds his leg is encircled by multiple garters which impair venous return even more Even storkings can cause difficulties especially those applied on the leg below the knee in which the upper edges are tight and act as garters The various problems concerned wit the use of stockings bandaging and full support is not emphasized sufficiently The panty hose type custom fit are certainly worth serious consideration for venou support in the legs This i a highly recommended book

Hypertens on and Stroke Control in the Community Edited by S Hatano I Shigematsu and T Strasser Geneva 19 6 World Health Organization 36? pages Price $1? 00

This is the proceedings of a WHO meeting held in Tokyo during March 19 4 on the control of hypertension and stroke The papers and discussions are good The statistical and epidemiologic data are interesting The problems of manage ment of mild hypertension and the community approach to the control of hypertension and stroke and their consequences are reviewed very well The sections of the book concerning the discussions among the participants are most interesting This publication summarizes very well the WHO programs and recommendations on hypertension and stroke based on a statistical and epidemiological point of view as well as the clinical.

Qu ck Reference to Card ovascular D seases Edited by Edward K Chung Philadelphia 19 7 J B Lipp ncott Company 469 pages. Price $20 00

This book edited by Chung is an interesting and useful presentation of clinical cardiology in a brief condensed manner There are 36 contributors to this publi ation all capable card ologists The diseases and problems di cussed are the comm n ones encountered by clinicians daily Each contribution is written concisely and in a summary type approach The references cited are well chosen and again clinically oriented This reviewer is of the opinion that the outline manner of describing the clinical problems will require a great deal of supplemental reading in order to understand better the symptoms signs management drug action and other phases of the illnesses For those who are well informed the manner of presentation is extremely useful for a rapid review of the various common clinical problems. Diagnosis, pathophysiology and management are empha sized This is a recommended and u eful addition to the cardiologic literature The busy practicing physician will especially appreciate this publication

Microcirculation Blood vessel Interactions Systems in Special Tissues volume I Edited by John Grayson and Walter Zingg New York 1977 Plenum Press 4?0 pages Price $3? 00

Volume I of Microcirculation edited by Grayson and Zingg represents the proceedings of the First World Congress for the Microcirculation held in Toronto June 15 to 20 19?? As with other proceedings of symposia this one contains the papers presented at the meetings The 1?9 presentations are briefly and well summarized in one to two pages each These brief presentations which are essentially abstracts make it possible for the reader to obtain the essential aspects of the studies. The reader can then follow up his interest by contacting the authors for further information or he can approach the literature directly and more extensively The subjects discussed were quite numerous and include several presentations on blood and blood vessel interaction methods red cell interactions with the microcirculation blood vessel structure microcirculatory flow patterns formed elements of the blood platelets and thrombosis lymphatics pulmonary circulation myocardial blood flow splanchnic circulation skeletal muscle and the microcirculation in other tissues The papers are well written and present nicely the important aspects of the studies in a concise manner This book certainly will be welcomed by busy readers. Those readers who are interested in details of technic and results will be forced to resort to further sources of information This is a highly recommended publication on a much neglected important subject

Diagnosis and Management of Medical Emergencies second ed tion Edited by Rustom Jal Vakil M D and Farokh Erach Udwadia M D New York 1977 Oxford University Press 50 pages Price $?4 00

This second edition of Diagnosis and Management of Medical Emergencies" should interest cardiologists since cardiac problems are frequently responsible for the medical emergencies encountered in med cal practice Emergency room physicians will find the book useful The 6 chapters include among the many types of medical emergencies cardio vascular respiratory shock, and industrial and accidental emergency states The many contributors mainly from Bombay India include diagnosis and differential diagnosis along with management As the pace of living industrial activity and aging of people increase emergency treatment is becoming more and more important in the practice of medi cine This somewhat encyclopedic book is a useful publication that is entirely clinically oriented This second edition continues to be an important publication in medicine and is recommended as a reliable practical book for cardiologists who are so often consulted to assist in the management of emergency disease states

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American Heart Journal

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Editorial

International cardiology

J F Goodwin M D *
London England

Cardiology developed at a rapid pace in the immediate years following the Second World War as a result of introduction of techniques of cardiac catheterization and angiocardiography and of the growth of cardiac surgery These developments were aided by improvements in communication and by easier methods of travel which went towards meeting the increasing needs of scientists in all countries to exchange information At the same time the developing countries were urgently in need of help with training programs cardiological education and with identification of priorities in tackling these and allied problems

The increasing incidence of cardiovascular disease especially coronary artery disease emphasized the necessity of collaboration among nations in developing programs of prevention and treatment and also the need for meetings to discuss and share the results of research The continuing incidence of severe rheumatic heart disease in the developing countries imposed an important claim on available resources

Even before the Second World War the need for international meetings was demonstrated by the gathering of a group of internationally known cardiologists in Prague in 1933 This was followed in 1944 by the Congress of the Inter American Society of Cardiology in Mexico City at the time of the foundation of the Institute of Cardiology The Director Dr Ignacio Chavez invited a number of internationally famous cardiologists including Drs Paul White Samuel Levine Carl Wiggers and Louis Katz from the USA In 1946 the first International Council of Cardiology was formed and was charged with the task of laying the foundations of an International Society and with organizing the First World Congress of Cardiology to be held in 1950 Among the members of the Council were Sir John Parkinson of Great Britain Professor Laubry of France Professor Gustav Nylin of Sweden Dr Paul White of Boston and other distinguished cardiologists

The European Society of Cardiology was founded in 1947 on the occasion of the Third Inter American Congress of Cardiology in Chicago

The First World Congress of Cardiology was held in Paris in 1950 under the Presidency of Professor Laubry One thousand cardiologists attended and 486 scientific papers were presented These were very small numbers by present standards but it was a noble beginning The International Society of Cardiology (ISC) was formed at this time with the following statutes

1 To stimulate the development of Cardiology in all its aspects application instruction research prevention of cardiovascular disease help to cardiologists and help to cardiac patients

2 To improve scientific exchange as well as technical and material cooperation between the affiliate societies of cardiology

3 To contribute to the scientific development of its members and to the maintenance of ethical standards in the exercise of the specialty

4 To organize and support courses confer

From the Royal Postgraduate Medical School London England

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Books received

Long term Surgical Results in Children Progress in Pediatric Surgery vol 10 Edited by P P Rickham W Ch Hecker and J Prévot Baltimore 1977 Urban & Schwarzenberg 303 pages Price $29 50

Biofeedback & Self control 1976/77 An Aldine Annual on the Regulation of Bodily Processes and Consciousness Edited by Joe Kamiya T X Barber Neal E Miller David Shapiro and Johann Stoyva Chicago 1977 Aldine Publishing Company 597 pages

Microvascular Reconstructive Surgery By Bernard McC O Brien B Sc M S F R C S Churchill Livingstone New York 1977 350 pages Price $38 00

Pediatric Echocardiography By Richard A Meyer M D with chapters by Russel L Uphoff B S and with the assistance of Joan Korfhagen R D M S Philadelphia 197- Lea & Febiger Publishers 303 pages Price $1- 00

Infant and Child Care in Heart Surgery By Robert M Sa- M D Delos M Cosgrave M D and Aldo R Castaneda M D Chicago 1977 Year Book Medical Publishers, Inc 1-- pages

Trends in Computer processed Electrocardiograms Edited by J H van Bemmel and J L Willems Amsterdam, The Netherlands 1977 North Holland Publishing Co 430 pages Price $46 95

Sang et Toxiques Collection de Médecine Légale et de Toxicologie Medicale XVes Journées du Groupement Français des Centres Anti Poisons Paris 19-- Editions Masson 220 pages

Announcements

Recent Advances in Cardiopulmonary Care IV

A seminar entitled Recent Advances in Cardiopulmonary Care IV sponsored by Memorial Hospital Sarasota Fla will be held on March 2 and 3 1978 at the Holiday Inn Lido Beach Sarasota Registration fees are $50 for physicians and $40 for nurses and others Twelve contact hours of continuing education units (CEU s) will be given

For further information regarding this seminar please contact Human Resources Development Department Memorial Hospital 1901 Arlington St Sarasota Fla 33579 Telephone (813) 959 1767

Seventh Annual Cardiology Symposium

The Johns Hopkins Medical Institutions announces that the Seventh Annual Cardiology Symposium A Review of Changing Concepts Current Management and New Techniques and Therapies will be held June 1 through 3 1978 at the Cross Keys Inn Baltimore Maryland For further information contact Dr J O Neal Humphries Carnegie 568 The Johns Hopkins Hospital Baltimore Maryland 21205

Geriatric seminar

A seminar entitled Geriatric Pow Wow will be conducted on April 7 through 9 1978 at the Arizona Inn 2200 E Elm St Tucson Ariz 85719 under the auspices of the University of Arizona College of Medicine Office of Continuing Medical Education This seminar is accredited by the Council on Medical Education of the American Medical Association for 16 Category I credit hours For further information please contact Office of Continuing Medical Education (Attn Katharine Blosch) University of Arizona College of Medicine Arizona Health Sciences Center Tucson Arizona 85724 Telephone (602) 882 6173

The Lucien Dautrebande prize

The Fondation de Physiopathologie Professeur Lucien Dautrebande will award its next prize of about ,000,000 Belgian francs in 1979 The award will be presented for a work on human or animal clinical physiopathology preferably having therapeutic implications Applicants must submit their candidature before December 15 1978 to be considered for the award For further information regarding this competition please write Office of the Fondation de Physiopathologie Professeur Lucien Dautrebande 35 chaussée de Liège 5200 Huy Belgium

National Symposium on Aging

The University of California San Francisco Schools of Dentistry Medicine Nursing and Pharmacy and the Division of Continuing Education Health Sciences, present a two-day symposium entitled "The National Symposium on Aging" to be held on February 25 and 26 1978 in San Francisco For further information please contact Program Chairman National Symposium on Aging Division of Continuing Education Health Sciences Univ of Cal San Francisco Cal 94143

Information for authors

Most of the provisions of the *Copyright Act of 1976* became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following statement signed by each author The undersigned author(s) transfers all copyright ownership of the manuscript entitled (title of article) to The C V Mosby Company in the event the work is published The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published Authors will be consulted when possible regarding republication of their material

Foundations explaining the reasons for the merger and asking them to approve it All the replies that were received were in favor Simultaneously the International Cardiology Federation circularized all its National Foundation members and received similar replies

The merger was thus confirmed at the Long Range Planning Committee meeting in November 1976

The Assembly of the ICF agreed to dissolve at its meeting in January 1977 on the understanding that the Assembly of the ISC would do likewise in Tokyo in 1978 at the Eighth World Congress of Cardiology Because of the difference in timing of the Assemblies of the two organizations the ISFC could not be finally ratified on a permanent basis for a further 20 months It would thus for practical purposes work entirely as a single society in order to promote its objectives and in particular to encourage and maintain the work of the Scientific Councils and the lay education programs The ISFC was notified as a new society under Swiss Law in Geneva in early January 1977 and the first meeting of the Joint Executive Board was held in London in February 1977 The names of the Executive board are as follows

President Professor John Goodwin M D Great Britain
1st Vice President Dr N J C M Kappeynee van de Copello The Netherlands
Immediate Past President Dr Lysle Peterson M D U S A
Past 1st Vice President Dr L E January M D U S A
Administrative Secretary Mr K Meister Denmark
Medical Secretary Dr Pierre Moret M D Switzerland
Treasurer Mr E MacDonald Canada
Chairman of the Scientific Board Professor Franz Gross M D W Germany
Chairman of the Public Education Committee Mr Finn Monahan Eire
President of the Asian Pacific Society of Cardiology Dr Morton Berk M D U S A
President of the European Society of Cardiology Dr H Denolin M D Belgium
President of the Inter American Society of Cardiology Dr E Hirschaut M D Venezuela
Chairman of the Financial Support Committee To be appointed

It is a pleasure to acknowledge the important work of Dr Lysle Peterson when President of the ISC and of Mr Kappeyne when President of the ICF in promoting the merger Without their tireless work and patience the merger might never have been achieved so that international cardiology is much in their debt

The immediate aims of the ISFC are to raise sufficient funds to maintain its programs and the administration necessary to direct and support them and to sponsor and assist in every way possible the activities of the Scientific Councils and the Public Education Committee Clearly these activities cannot be sustained without adequate funds Financial support must be raised by subscription from the national Societies and Foundations which are members of the ISFC In return the ISFC will perform important functions in the realms of scientific communication lay education and sponsorship of meetings Funds are necessary to support the Scientific Councils in their functions of research and teaching and also the Public Education Committee A good example of the work of the latter is the World Hypertension Year 1978 which is an exercise in public education supported by WHO The Scientific Councils are intensely active and organize their own workshops and teaching programs Where appropriate multicenter collaborative research programs are mounted such as that on Congestive Cardiomyopathy organized by the Council on Cardiomyopathy

The formation of the Scientific Councils of the International Society of Cardiology from the original research committee was an important and significant event which took place at the Fifth World Congress of Cardiology in New Delhi in 1966 At the present time seven Scientific Councils make up the Scientific Board which is under the Chairmanship of Professor Gross of Heidelberg The Councils are as follows

1 Arteriosclerosis and Ischaemic Heart Disease Chairman Dr G Schettler (West Germany)
2 Council on Cardiomyopathies Chairman Dr E Olsen (Great Britain)
3 Council on Epidemiology and Prevention Chairman Dr J Stamler (U S A)
4 Council on Hypertension Chairman Dr J I S Robertson (Great Britain)
5 Council on Paediatric Cardiology Chairman Dr K Bossina (The Netherlands)
6 Council on Rehabilitation of Cardiac Pa

ences, publications and other activities deemed necessary for the realization of the aims noted above

5 With the same objectives, to sponsor World Congresses of Cardiology every four years

These statutes have not changed substantially in the last 25 years

Since 1950 World Congresses of Cardiology (as everyone knows) have been held every four years, the Eighth being due in Tokyo in 1978 The European Society of Cardiology has held its congresses also every four years two years between each World Congress The Inter American Society also holds Congresses in the same year as the European Society The Asian Pacific Society of Cardiology, which was formed in 1956 at the suggestion of Dr White holds its Congresses in the same year as the European and Inter-American Societies

Thus there were in 1976 three continental societies and one world society in addition to many national societies affiliated to the International and appropriate regional Continental Societies In addition the American Heart Association provides the United States of America and the World with a vital active, and thriving combined Cardiac Society and Foundation The inauguration of the American College of Cardiology in 1975 provided a further stimulus for education teaching and research on both national and supra national levels

In 1957 the International Cardiology Foundation was created as a lay organization with medical membership to promote lay education in cardiovascular disease and to raise funds for the advancement of cardiology throughout the world In 1970 the International Cardiology Federation (ICF) was formed from the Foundation with the responsibility of raising funds for the scientific programs of the International Society of Cardiology and of stimulating the growth of national Cardiology Foundations The formation of the International Cardiology Foundation was largely due to the imagination and enterprise of Dr Paul White Mr Albert Baer of New York played a considerable part in fund raising at that time

The membership of the International Cardiology Federation was composed of National Heart Foundations

In 1970 at the Sixth World Congress of Cardiology in London the proposal for a merger between the ISC and the ICF was discussed Dr White strongly stressed the wisdom of allowing experienced laymen to assume responsibilities of fund raising and public relations It was felt that the merger would greatly facilitate the work of both organizations and should provide a joint Society which would combine fund raising and educational activities with the promotion of research into the preventive, diagnostic, and therapeutic aspects of cardiovascular disease However it was not until 1974 that arrangements for the merger were seriously discussed In the intervening years the International Society of Cardiology was in receipt of generous support from the American Heart Association and from the Canadian Heart Foundation, in addition to subscriptions from many, though unfortunately not all national cardiac societies Because of the financial problems of maintaining the basic organization necessary to promote its aims the ISC was not always able to allocate sufficient funds to maintain the work of the Scientific Councils and financial problems tended to multiply

At the Seventh World Congress in Buenos Aires in September, 1974 the Assembly of the International Society of Cardiology agreed to the principle of a merger and directed that the details be worked out by a Long Range Planning Committee which was composed of representatives both of the ISC and the ICF After numerous discussions in the ensuing months the terms of the merger were drawn up and the proposed statutes and bylaws were circulated to National Societies and Foundations The statutes and bylaws did not differ materially from those already in existence It was suggested that the merged organization should be essentially a medical scientific body dedicated to the promotion of world cardiology by stimulation of research teaching lay and professional education and the encouragement of preventive aspects of cardiology Fund raising and public relations would be important aspects also The President would be medically qualified and although there would be a preponderance of medically qualified members on the Executive Board at all times there would be important members such as the First Vice President Administration Secretary, the Treasurer, and Chairmen of the Public Education Committee who would not be medically qualified

It was agreed that the merged organization should be called the International Society and Federation of Cardiology (ISFC) and a request was sent in mid 1976 to all National Societies and

Sequence of cardiac changes in Duchenne muscular dystrophy*

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Pathologic examination of the heart in boys dying after age 12 with Duchenne muscular dystrophy (DMD) invariably shows marked left ventricular interstitial fibrosis and extensive replacement of myocardial fibers with connective tissue[1-4] Heart failure is a common terminal manifestation of the disease Clinical evidence of heart disease however is rare until shortly before death and even then is usually precipitated by penumonia

Cardiovascular physical examination is complicated by the presence of chest deformities especially in boys over 12 Nevertheless several possibly abnormal signs have been described Tachycardia is a frequent finding but its relationship to age and stage of skeletal muscle disease has not been defined Left parasternal impulses occurred in about half of the 35 DMD boys in Perloff and colleagues series but were associated with normal right ventricular and pulmonary arterial pressures and were therefore attributed to chest deformity Most DMD patients have a third heart sound but up to age 30 this may be normal Atrial gallops have been described in about one third of DMD patients[1]

Chest x ray examination reveals the straight thoracic spine and occasionally a pectus excavatum with resultant pancake heart These skeletal deformities make interpretation of the cardiac silhouette difficult especially since they are most prominent in the end stages of the disease Only two patients in Perloff and colleagues series[1] had clear evidence of cardiomegaly one of these died in cardiac failure shortly thereafter

In contrast to physical examination and chest x ray the electrocardiogram reveals disturbances of electrical function in up to 90 per cent of patients[1, 3] and has been used as a diagnostic criterion for DMD Tall R waves are present in Lead V_1 and deep narrow q waves are found most frequently in Leads V and V_6 These changes do not appear to be related to age duration of disease or disability

Echocardiography has been used by Kovick and associates[5] to study left ventricular wall motion in patients with different types of muscular dystrophy These subjects had a significantly slower rate of diastolic relaxation of the left ventricular posterior wall than normal controls although the degree of abnormality did not correlate with age type or severity of dystrophy

Cardiac catheterization has been useful in detecting latent cardiac dysfunction[1] In Perloff and colleagues series abdominal compression in 70 per cent of subjects of unspecified age caused an abnormal rise in right atrial or right ventricular end diastolic pressure possibly indicative of early cardiac dysfunction Wahi and coworkers found abnormal left ventricular dp/dt and end diastolic pressure in all of five Duchenne patients evaluated by left heart catheterization who had abnormal electrocardiograms Again however age and extent of muscle disease were

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tients Chairman, Dr H Denolin (Belgium)

7 Council on Thrombosis and Haemostasis Chairman, Dr M Hardisty (Great Britain)

These Councils usually have about 20 members who are drawn from all parts of the World

At its first meeting the Executive Board of the ISFC formulated an active program of fund raising scientific work, public education and sponsorship of world meetings The ISFC of course, assumes responsibility for sponsorship of the World Congress of Cardiology in 1978 Advice on the Scientific Program and its organization is being given by the Chairmen of the Scientific Councils, the Chairman of the Scientific Board, and the President of the ISFC in collaboration with the organizers of the Congress in Tokyo

The President of the ISFC will meet the Presidents of the Continental Societies in mid 1977 to discuss the mutual relationship of these Societies, the coordination and promotion of world meetings and collaboration in research From this meeting it is hoped that better coordination of world events in cardiology will be achieved and better understanding of critical problems will result It should be possible to delineate areas of special need for research, teaching and education so that rational allocation of funds can be achieved

It is not surprising that, as the complexity of cardiological investigations and treatment increases, and as the exacting demands of advancing cardiovascular disease become more insistent, better cooperation and integration between international cardiological organizations become essential

The Bulletins of the ISC and ICF have been combined in the Journal Heartbeat which will give news of the National Societies and Foundations of Cardiology dates of meetings reports of Scientific Councils and of public education events Details of international meetings will be given regularly and in particular information about the Eighth World Congress of Cardiology in Tokyo in 1978 and of the progress of "World Hypertension Year, 1978" will appear from time to time

"The Year of the Merger" 1977, should herald a new era in International Cardiology and the active support and encouragement of cardiac Societies and Foundations all over the world will be needed and appreciated as an essential requirement for success

I am much indebted to Dr Vittorio Puddu Past President of the ISC for data on history of the ISC published in the Bulletin of the ISC at the time of the Sixth World Congress of Cardiology in 1970 I am also indebted to Mme Marianne de Figueiredo for material on the history of the ICF

included in the examination Pericardial-epicardial echoes were identified with a low gain setting and then the gain was increased until the endocardial echo was located The record was obtained on heat sensitive paper at a speed of 50 mm per second using a Tektronix recorder In each record five different complexes were analyzed according to the method of Feigenbaum and the average values were calculated for the following variables diastolic internal diameter (mm) (LVIDd) systolic internal diameter (mm) (LVIDs) diastolic left atrial diameter (mm) (LADd) systolic left atrial diameter (mm) (LADs) diastolic aortic diameter (mm) (AOd) systolic aortic diameter (mm) (AOs) diastolic right ventricular internal diameter (mm) (RVIDd) diastolic posterior left ventricular wall thickness (mm) (WALLd) systolic posterior left ventricular wall thickness (WALLs) interventricular septal thickness (mm) (IV SEPT) and interventricular septal excursion (mm) (IVSE) In the three DMD patients with chest deformities the average value of the long (suprasternal view) and short (standard view) axis of the left atrium was used to calculate LADd and LADs The following were calculated from the echogram dimensions collected on each subject as follows

End diastolic volume = (LVIDd) × 1 05

End systolic volume = (LVIDs) × 1 05

Ejection fraction (EF) = stroke volume/end diastolic volume

Stroke index (SI) (c c /M) = end diastolic volume – end systolic volume/BSA

Cardiac index (CI) (liter/min /M) = heart rate × (stroke index/1000)

Posterior LV wall excursion (mm) (WALLE) = maximum amplitude of systolic LV wall excursion

Per cent fractional shortening of the internal dimension from end diastole to end systole (%)

$$(\%LV) = \frac{LVIDd - LVIDs}{LVIDd} \times 100$$

Maximal systolic and diastolic endocardial velocities (SEVM DEVM) were determined according to the method of Kovick and associates which consists of drawing a tangent to the steepest portion of the systolic or diastolic endocardial excursion and measuring the slope in mm/sec The mean rate of circumferential fiber shortening (Vcf) was determined by measuring ejection time (LVET) from the carotid pulse tracing (time between initial carotid upstroke and the dicrotic notch at the completion of the echocardiogram) and calculated according to the following equation

$$Vcf\ (circ\ \ sec\ \ ) = \frac{LVIDd - LVIDs}{LVET \times LVIDd}$$

Table I Comparison of DMD boys and control subjects matched according to age and BSA Values represent means ± S D

	DMD (N = 18)	Controls (age matched) (N = 18)	Controls (BSA matched) (N = 18)
Age	11 9 ± 3 3	11 8 ± 3 4	10 1 ± 3 6
BSA(M)	1.21 ± .31	1.34 ± .30	1 21 ± .3?

P < 0 f r comparison of specified control v l with the correspond ing DMD value

Results

The results of matching the 18 DMD boys to 25 control subjects (Table I) reveal the differing relationship between age and body surface area (BSA) in the two groups Healthy boys matched with respect to age had a greater BSA than their DMD counterparts In contrast healthy subjects matched on the basis of BSA were younger than their DMD opposite members

The results of physical examination electrocardiogram chest x rays SCPK and its isoenzymes and echocardiography are presented for both controls and patients in Table II The results are given for either the age or BSA match whichever provided the higher correlation with the variable under consideration in the normal boys For the dimensions independent of age and BSA the age match is presented

The DMD boys were divided into early (age 4 to 10 years) and late DMD (age 9 to 17 years) on the basis of MMT ($\geq$ 50 per cent and $<$ 50 per cent respectively) As Table II shows 26 types of cardiac measurement were made on each DMD child (physical examination one ECG two chest x ray one serum enzymes three echocardiography 19) In the normal boys serum enzyme levels were not measured

In control subjects eight of the 23 measurements were independent of age ΣQ/ΣR CI SI EF %LV IVSE Vcf and SEVM The other 15 measurements showed a significant (P < 05)

not specified In addition these procedures are invasive and medically unjustified in most DMD subjects

Thus, while every patient with advanced DMD who has come to autopsy has had dystrophic heart disease the natural history of this process during life has remained obscure because its progress is almost undetectable by conventional cardiovascular techniques Echocardiography is a relatively new, non invasive method utilizing reflected ultrasound for determining cardiac structure and function and is ideally suited to the study of dystrophic heart disease This technique has been utilized in the present study to evaluate cardiac involvement in Duchenne muscular dystrophy patients

Materials and methods

The subjects were 18 boys with Duchenne dystrophy aged 4 to 17 years randomly selected from 45 under observation at the Emory Muscular Dystrophy Clinic, and 25 healthy boys Diagnosis of Duchenne dystrophy was based on progressive weakness over a 3 to 7 year period of observation particularly apparent in neck flexor abdominal flexor gluteus maximus and medius, middle trapezius and rhomboid musculature, pseudohypertrophy of the calves, onset of symptoms before age 8 positive family history in brothers and male maternal relatives elevated serum concentrations of creatinine phosphokinase lactic dehydrogenase and glutamic oxaloacetic transaminase electromyographic evidence of myopathy and confirmatory muscle biopsy in the patient or in an affected male relative

Each DMD subject was hospitalized and underwent the following examinations Cardiovascular physical examination muscle function testing ECG, chest x ray serum (iso)enzymes (CPK) and echocardiogram The patient was then matched with two controls one by age (± 1 year) and one by body surface area (± 0 1 M) Control subjects underwent as outpatients a series of examinations similar to those administered to the DMD boys

Physical examination A cardiovascular physical examination was performed In order to quantify the degree of musculoskeletal involvement manual muscle testing was performed on each patient and the result expressed as the per cent of normal muscle function remaining Each muscle group was assigned a numerical value as follows 5 = Full range of motion against gravity with strong resistance 4 = Full range of motion against gravity with moderate resistance 3 = Full range of motion against gravity no other resistance, 2 = Full range of motion gravity eliminated, 1 = No motion but visible or palpable contraction and 0 = No visible or palpable contraction The manual muscle test (MMT) score obtained by summing the weighted results of all muscle groups was divided by the total points obtainable for normal function and expressed as a per cent of normal A score of 100 per cent represents normal function, while a score under 40 per cent represents severe musculoskeletal dysfunction

EKG A standard 12 lead electrocardiogram was done on each subject, and the following measurements made (a) the ratio of the R to the S wave in Lead V_1 ($R/S\ V_1$) was calculated and (b) q waves if present in Leads I, II, or V_6 were measured and expressed as a ratio to the R wave in that lead (Q/R) The Q/R ratio in the three leads was then summed and expressed as a single value, $\Sigma Q/\Sigma R$

Chest x ray Standard six foot posteroanterior and lateral views were obtained for each patient and the two views were used to calculate heart volume[11] This was then corrected for body surface area and expressed as the heart volume index (HV index)

Enzymes Serum creatinine phosphokinase (SCPK) concentration of each patient was determined To gather information regarding a cardiac or skeletal source of this enzyme SCPK was further separated into its isoenzyme fractions MM CPK (skeletal muscle) BB CPK (brain) and MB CPK (heart)

Echocardiogram The echocardiograms were performed with a Unirad echograph employing a 2 25 MHz 0 5 inch diameter transducer with either a 10 cm or 7 5 cm focus The transducer was placed in the fourth or fifth left intercostal space close to the sternum and the mitral valve was located The transducer was then aimed inferiorly and laterally just below the anterior leaflet of the mitral valve in order to obtain simultaneous echoes of the interventricular septum and posterior left ventricular wall If pectus excavatum or straight thoracic spine was present an additional suprasternal approach was

included in the examination Pericardial-epicardial echoes were identified with a low gain setting and then the gain was increased until the endocardial echo was located The record was obtained on heat sensitive paper at a speed of 50 mm per second using a Tektronix recorder In each record five different complexes were analyzed according to the method of Feigenbaum and the average values were calculated for the following variables diastolic internal diameter (mm) (LVIDd) systolic internal diameter (mm) (LVIDs) diastolic left atrial diameter (mm) (LADd) systolic left atrial diameter (mm) (LADs) diastolic aortic diameter (mm) (AOd) systolic aortic diameter (mm) (AOs) diastolic right ventricular internal diameter (mm) (RVIDd) diastolic posterior left ventricular wall thickness (mm) (WALLd) systolic posterior left ventricular wall thickness (WALLs) interventricular septal thickness (mm) (IV SEPT) and interventricular septal excursion (mm) (IVSE) In the three DMD patients with chest deformities the average value of the long (suprasternal view) and short (standard view) axis of the left atrium was used to calculate LADd and LADs The following were calculated from the echogram dimensions collected on each subject as follows

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Table I Comparison of DMD boys and control subjects matched according to age and BSA Values represent means ± S D

	DMD (N = 18)	Controls (age matched) (N = 19)	Controls (BSA matched) (N = 16)
Age	119 ± 33	118 ± 34	101 ± 36
BSA(M)	1 21 ± 31	1 34 ± 30	1 21 ± 3[illegible]

P < 05 for comparison of specified control value with the corresponding DMD value

ejection time (LVET) from the carotid pulse tracing (time between initial carotid upstroke and the dicrotic notch at the completion of the echocardiogram) and calculated according to the following equation

$$Vcf\ (circ\ sec^{-1}) = \frac{LVIDd - LVIDs}{LVET \times LVIDd}$$

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In control subjects eight of the 23 measurements were independent of age ΣQ/ΣR CI SI EF %LV IVSE Vcf and SEVM The other 15 measurements showed a significant (P < 05)

Table II Summary of cardiac measurements in DMD[1]

		Total						Early DMD[a]					
		Controls			DMD			Controls			DMD		
	Match	Pairs	$\bar{X}$	SD	N	$\bar{X}$	SD	Pairs	$\bar{X}$	SD	N	$\bar{X}$	SD
Physical examination													
HR	age	18	64 0	10 8		90 5‡	13 1	9	73 1	11 5		91 [illegible]	[illegible]
Electrocardiogram													
R/S V	age	18	46	35		1 32‡	81	9	67	37		1 12‡	[illegible]
ΣQ/ΣR	age	18	04	07		37‡	42	9	07	1		37‡	[illegible]
Chest x ray													
HV index (c c /M)	age	18	323 8	55 7		395 2†	128 0	9	300 0	51 0		3[illegible]9	6
Serum enzymes													
SCPK (units)					18	3961 1	3158 0				9	[illegible]	[illegible]
MM CPK (units)					16	3403 0	2820 0				8	[illegible]061 0	[illegible]
MB CPK (units)					16	502 8	849 6				8	[illegible]	[illegible]
Echocardiogram													
A Anatomy													
LV WALLd (mm)	BSA	18	6 5	1 5		6 6	1 5	9	5 9	1 4		5 9	
LV WALLs (mm)	BSA	18	11 2	2 3		10 4†	1 6	9	10 3	1 9		9 8	11
LV IV Sept (mm)	BSA	18	7 7	1 5		7 2	1 5	9	7 1	1 5		6 5	11
LV LVIDd (mm)	BSA	18	41 2	6 1		40 2	5 4	9	39 3	6 9		3[illegible]9	[illegible]
LV LVIDs (mm)	BSA	18	27 1	3 9		28 7	5 2	9	25 7	4 3		[illegible]	[illegible]
LA LADd (mm)	BSA	18	18 6	3 8		17 8	5 0	9	16 7	3 4		1[illegible]	[illegible]
LA LADs (mm)	BSA	18	24 4	4 7		24 7	5 4	9	23 0	3 7		[illegible]3	[illegible]
AO AOd (mm)	BSA	18	21 1	3 2		20 9	1 6	9	20 2	2 5		[illegible]	[illegible]
AO AOs (mm)	BSA	18	23 8	3 3		23 3	2 3	9	23 1	3[illegible]		[illegible]3	[illegible]
RV RVIDd (mm)	BSA	8‖	11 3	3 9		9 8	3 2	—					
B Function													
SI (c c beat/M)	age	18	45 1	13 7		37 0†	9 3	9	40 0	12 3		3[illegible]4	[illegible]
CI (L /min /M)	age	18	3 0	9		3 4	1 3	9	3 2	9		3 6	[illegible]
EF	age	18	71	05		63‡	08	9	72	04		6	[illegible]
%LV ( )	age	18	33 9	3 8		28 9‡	4 7	9	34 0	3 9		31 1	[illegible]
WALLE (mm)	BSA	18	9 7	1 6		7 5§	1 5	9	9 2	9		6‡	[illegible]
IVSE (mm)	BSA	16	7 0	9		6 1†	1 0	8	7 2	5		[illegible]	[illegible]
DFVM (mm /sec)	age	18	127 6	25 7		80 5§	27 4	9	116 5	17 3		89 6†	[illegible]
SEVM (mm /sec)	age	18	42 2	7 6		38 8	7 9	9	34 8	10 7		42 6	[illegible]
V (cm /sec)	age	15	1 08	13		1 04	18	7	1 10	14		1 [illegible]0	[illegible]

P values by paired t test indicate statistical difference
P < 1
†P < 05
‡P < 01
§P < 001
‖Includes those pairs in whom both members had an RVIDd of technically good quality and if normal chest configuration was present
a Manual muscle test ≥ 50%
b Manual muscle test < 50%

linear relationship both with age and with BSA The regression equations describing the relation of 14 of these variables with age or BSA are given in Table III for control subjects and DMD youngsters

When the entire DMD group was compared with the entire control group 11 of the 23 measurements showed a statistically significant difference HR R/S V, ΣQ/ΣR HV index, WALLs SI EF %LV, WALLE, IVSE, and DFVM Contrastingly when this comparison was made in the patients with early DMD and their matched controls only six of 23 cardiac measurements different significantly heart rate R/S V, ΣQ/ΣR WALLE IVSE and DFVM In the late DMD subgroup these six variables showed even more marked deviations from normal and in addition significant differences from matched controls had now appeared in five other cardiac indices HV index EF %LV SEVM and Vcf

Late DMD'					
	Controls		*DMD*		
Pairs	$\bar{X}$	*SD*	*N*	$\bar{X}$	*SD*
9	57 ?	8		89 3‡	8 8
9	8	??		1 50‡	1 0
9	03	01		36	55
9	347 7	51		4?6 ‡	116 0
			9	19?9 0	91 0
			8	1?4? 0	8? 0
			8	100 5	113 0
9	?	1 4		? 3	1 ?
9	1? 2	? 4		11 0	1 ?
9	8 ?	1 3		9	1 4
9	43 1	5 0		4? 5	5 9
9	?8 5	9		31 3	5 6
9	?0 6	3 4		18 8	5 5
9	?6 4	4 9		? ?	6 9
9	??0	? ?		1	1
9	4 6	? 8		?4 6	1 3
9	46 ?	15 7		38 8	9 8
9	8			3 2	1 0
9	0	06		60	09
9	33 8	3 8		?6 6‡	5 3
9	10 ?	? 0		? 5‡	1 8
8	6 8	1 ?		6 3	1 0
9	138 7	28 7		71 4‡	31 1
9	38 6	4 8		4? 5†	3 8
8	1 06	1?		93†	18

A more detailed view of several indices which were significantly abnormal in the DMD group is given in Fig 1 HR R/S V $\Sigma Q/\Sigma R$ SCPK and MB CPK WALLE and DEVM In these graphs every DMD boy is shown together with his matched control

Fig 1 *A* HR heart rate showed a significant inverse relation with age in the controls in DMD an inverse relation with age was also evident but for a given age the heart rate of DMD boys was faster than those of their matched controls

Fig 1 *B* R/S V in normal boys the ECG R/S ratio in Lead V decreased with age In DMD patients no such age relationship was evident Furthermore 78 per cent (14/18) of the DMD boys had a greater R/S V, ratio than the upper limit of normal for their age

Fig 1 *C* $\Sigma Q/\Sigma R$ this value was $< 0 2$ in 89 per cent of normal boys and did not vary with age In DMD $\Sigma Q/\Sigma R$ exceeded 0 2 in 65 per cent of patients and exceeded the value of the age matched control in 72 per cent of cases No relation to age was evident

Fig 1 *D* Muscle enzymes were abnormally elevated in all DMD patients There was a pro gressive decline in total and cardiac (MB) CPK with loss of muscle function (MMT)

Fig 1 *E* LV wall excursion increased with BSA in normal boys Although a similar relationship held in DMD patients the latter group generated a subnormal line in which WALLE was lower for any given BSA In 89 per cent (16/18) of DMD boys WALLE was lower than that of the BSA matched control

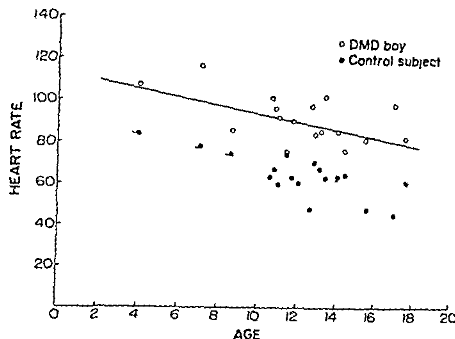
Fig 1 *F* DEVM increased with age in normal subjects but in DMD this function decreased with age In 89 per cent (16/18) of DMD boys the DEVM was lower than in the age matched control

In order to determine if there was a significant relationship between cardiac involvement and skeletal muscle disease severity we performed re gression analysis of each of these 11 indices against MMT In no case was there a significant correlation ($P < 05$) although ΔDEVM (Δ DEVM = value expected for age [72 4 + 4 9 (age)] – observed DEVM) was of borderline significance ($r = 0 4$ $P = 06$)

The echogram of a 12 year old DMD boy (MMT 42 per cent) and his BSA matched control are presented in Fig 2 The systolic excursion of the LV endocardium (WALLE) is reduced and the maximal systolic and diastolic endocardial velocities are slower in the DMD boy

Discussion

Summary of the findings Two technical factors concerning echocardiography should be considered before physiological significance is attributed to the observations made in DMD boys The first problem is that echocardiographic measurements of volume and function are based on an assumed geometric model of the heart pectus excavatum (PE) might compress the ventricle and invalidate these calculations In the present investigation only three subjects had PE



Figs 1A through 1E Examples of the cardiovascular abnormalities found in DMD subjects See *Results section* for further details A Heart rate versus age in DMD boys and age matched control subject The regression equations for all 25 control subjects and for 18 DMD boys are presented in Table III

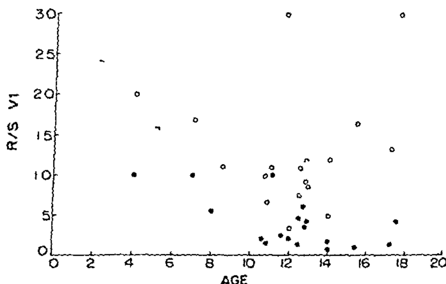


Fig 1B ECG R/S ratios in Lead V in DMD boys and age matched control subjects *The dashed line* represents the upper limits of normal for the R/S ratio in Lead V (The upper limits of normal are derived from Ziegler R Electrocardiographic standards in infants and children Springfield Ill 1951 Charles C Thomas Publisher)

(LDMD group) and furthermore six of the 11 abnormal indices were present in EDMD when no skeletal deformities were yet evident Thus PE did not contribute to most of the abnormal cardiac findings described The second consideration is that segmental myocardial disease could make echocardiographic calculations unreliable In DMD however the disease process as observed at autopsy usually has a symmetrical distribution with diffuse connective tissue and fat replacement and normal coronary arteries[1,2]

Accordingly we have calculated the various echo dimensions by the conventional equations[11] If however the early cardiac lesions have an asymmetric or segmental distribution our echocardiographic calculations will be correspondingly inaccurate Pending future clarification of this question the echo dimensions in *Table II* are therefore only tentative

The present investigation confirms the report of Kovick and colleagues[13] that DEVM is subnormal in subjects with muscular dystrophy

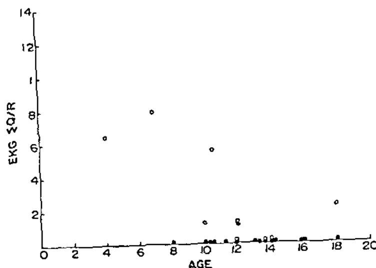


Fig 1C ECG ΣQ/ΣR in DMD boys and age matched control subjects

Table III Regression equations* relating age or body surface area to cardiovascular dimensions

	Control Subjects				DMD Subjects			
	N	Equation	r	P†	N	Equation	r	P†
Heart rate	25	= 89 8 – 2 1 (age)	0 73	< 001	18	= 111 8 – 1 78 (age)	45	= 05
HV index	25	= 195 5 + 11 7 (age)	0 80	< 001	18	= 189 6 + 1, 1 (age)	0 54	< 05
WALLd	25	= 2 6? + 3 2 (BSA)	0 79	< 001	18	= 3 14 + 2 8 (age)	0 59	< 01
WALLs	25	= 5 2? + 4 84 (BSA)	0 79	< 001	18	= 6 0 + 3 7 (BSA)	0 63	< 01
IV SEPT	25	= 4 78 + 2 39 (BSA)	0 60	< 01	18	= 3 64 + 3 0 (BSA)	0 69	< 01
LVIDd	25	= 22 0 + 15 0 (BSA)	0 79	< 001	18	= 26 5 + 11 5 (BSA)	0 66	< 01
LVIDs	25	= 13 5 – 10 7 (BSA)	0 78	< 001	18	= 18 5 + 9 3 (BSA)	0 45	= 05
LADd	25	= 4 8 + 2 4 (BSA)	0 60	< 01	18	= 6 8 + 9 3 (BSA)	0 60	< 05
LADs	?5	= 12 9 + 9 5 (BSA)	0 79	< 001	18	= 14 1 + 9 2 (BSA)	0 57	< 05
AOd	25	= 11 3 + 8 0 (BSA)	0 77	< 001	18	= 15 3 + 4 5 (BSA)	0 69	< 01
AOs	25	= 14 5 + 7 6 (BSA)	0 77	< 001	18	= 17 2 + 4 8 (BSA)	0 88	< 001
RVIDd	18	= 4 20 + 5 9 (BSA)	0 66	< 001	11	= – 7 + 11 7 (BSA)	0 5	< 1
WALLE	25	= 6 1 + 3 0 (BSA)	0 73	< 001	18	= 4 7 + 2 7 (BSA)	55	< 05
DEVM	25	= 72 4 + 4 9 (age)	0 79	< 001	18			Ns‡

Regressio eq tion d termined by the method of least squares
†P l f r correspo ding regressio eq tion
‡N = regress on eq tion not significant (P > 1)

including DMD Our present investigation extends this observation by defining the relation ship of DEVM to age in both DMD and normal boys and by identifying associated changes in Vcf SEVM WALLE and EF

The present data define two stages in the natural history of Duchenne heart disease Patients with *early DMD* compared to matched controls (Table IV) have a significantly (P < 05) faster heart rate greater R/S ratio in V_1 and q wave magnitudes elevated total and MB CPK diminished echogram LV wall and IV septal excursions and slower DEVM Boys with *late DMD* (Table IV) are characterized by the continued presence of these functional abnormal ities and now show in addition increased x ray heart volume index lower total and MB CPK and subnormal echogram EF %LV DEVM and circumferential fiber shortening Throughout the course of DMD heart disease while the above mentioned functional abnormalities appear and progress the anatomic dimensions of left ventric ular wall and septal thickness remain normal

Our goal must be to understand the mechanism for each of these abnormalities in cardiac behav ior Towards this end the possible mechanisms

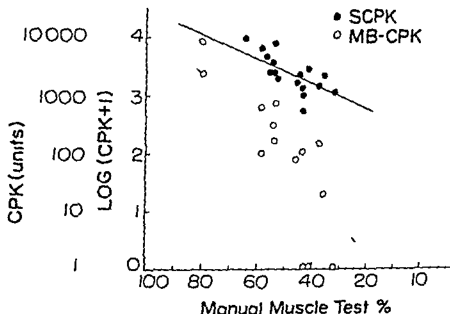


Fig 1D Total (SCPK) and MB CPK isoenzyme levels in DMD subjects versus age The regression equation for SCPK and MB CPK are log (SCPK + 1) = 2 42 + 0 021 (MMT) r = 0 71 P < 0 001 and log (MB CPK + 1) = 1 24 + 0 07 (MMT) r = 0 69 P < 0 05

Table IV Summary of cardiovascular examination in DMD patients

	Early DMD	*Late DMD*
Clinical examination		
1 Heart rate	↑↑	↑↑
2 Pectus excavatum		↑
Electrocardiogram		
1 R S V	↑↑	↑↑
2 q waves	↑↑	↑↑
Chest x ray		
1 Heart volume index	↑	↑↑
Serum enzymes		
1 CPK	↑↑↑	↑↑
2 MB CPK	↑↑	↑
Echocardiogram		
A Anatomy		
1 LV diastolic wall thickness	→	→
2 LV systolic wall thickness	↓→	↓→
3 LV internal dimensions	→	→
B Function		
1 Cardiac output	→	→
2 Stroke volume	↓	↓
3 Ejection fraction	↓	↓↓
4 % change in LV internal dimension	↓	↓↓
5 LV wall excursion	↓↓	↓↓
6 IV septal excursion	↓↓	↓
7 Maximal systolic endocardial velocity	↓	↓
8 Maximal diastolic endocardial velocity	↓↓	↓↓↓
9 Circumferential fiber shortening	↓	↓↓

↑ = increased above control boys
→ = no change
↓ = decreased below control boys

for each abnormal cardiovascular index identified in this study will be considered below

Possible mechanisms for each of the cardiac findings

Tachycardia was a feature of both early and late stages confirming earlier observation in DMD boys of unspecified age[1] Two mechanisms have been postulated

1 A circulating chronotropic agent e g thyroid hormone(s) or catecholamines has been suggested[1] although recent studies have failed to support this view[1]

2 An alternative hypothesis is that an early impairment in cardiac contractility caused a reflex tachycardia The present echocardiogram data support this mechanism by showing that impaired contractile function generally accompanied the tachycardia In both early and late DMD WALLE and DEVM were decreased compared to normal, furthermore in late DMD EF Vcf and SEVM were subnormal while RV index was increased All of these changes suggest defective contractility

EKG changes in this study as in others were present in > 90 per cent of DMD boys The most prevalent of these increased values for R/S V_1 and $\Sigma Q/\Sigma R$ were evident even in the youngest patients evaluated Four possible mechanisms have been suggested for the increased R/S in V_1 RV or septal hypertrophy impaired conduction and loss of posterior left ventricular electrical forces The present echo data provide direct

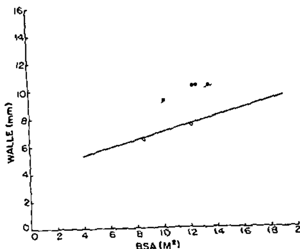


Fig 1E Posterior left ventricular wall excursion (WALLE) versus body surface area (BSA) in DMD patients and BSA matched control boys The regression equations for all 25 control subjects and for 18 DMD boys are presented in Table III

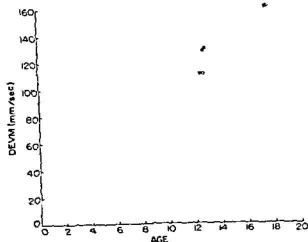


Fig 1F Maximal diastolic endocardial velocity (DEVM) versus age in DMD youngsters and in age matched healthy boys The regression equations for all 25 control subjects and for 18 DMD boys are presented in Table III

evidence against the first two hypotheses because RV and septal dimensions were normal The q wave phenomenon has been ascribed to diffuse necrotic zones creating electrically silent regions The present data shed no light on the pathogenesis of the abnormal q waves

Heart size by x ray appeared to be excessive in late DMD The chest deformities of late DMD introduce a possible technical error in radiographic heart volume calculations Nevertheless since the apparent cardiomegaly of late DMD was associated with several echocardiographic signs of impaired contractile function it probably represented the dilatation of early heart failure Because LV and septal wall thickness were not increased the cardiomegaly evidently manifested dilatation rather than hypertrophy The absence of LV hypertrophy in the echocardiogram dimensions of advanced DMD is not surprising in view of the extensive loss of muscle cells and deposition of fibrous tissue which are regularly present at autopsy

Serum enzymes The recognition of latent cardiomyopathy in DMD boys would be easier if the dysfunctional myocardial cell released a specific enzyme into the serum An obvious candidate for such a test is MB CPK This isoenzyme is specific for the heart in both normal and DMD subjects

Total CPK was markedly elevated in early DMD and declined progressively with age This confirms the findings of Pearce and colleagues and Okinaka and associates[19] who attributed the high initial value to diseased but viable skeletal muscle and the progressive decline to a continuing loss of skeletal muscle fibers from which CPK is derived The present study reveals a similar course for MB CPK The possibility arises therefore that this enzyme could serve as a qualitative indicator of the progression of cardiac DMD high MB CPK might indicate the early cardiac stage and a low or absent value might show late disease The validity of this notion awaits future testing

Echocardiogram abnormalities in early DMD (Table IV) were limited to a decrease in WALLE a smaller IVSE and a diminished DEVM Two possible mechanisms for these early abnormalities are (1) an adaptation to the tachycardia found in DMD boys and (2) impaired myocardial contractility

1 With regard to the first view the tachycardia of *exercise* or adrenergic stimulation is associated with *increased* WALLE and DEVM[2] WALLE and DEVM were *reduced* in DMD Thus this explanation is untenable

2 The second hypothesis proposes that decreased myocardial contractility results from myocardial fibrosis or from a molecular impediment to the contraction-relaxation process Cullen and Fulthorpe[20] have demonstrated hypercontracted muscle fibers in DMD skeletal

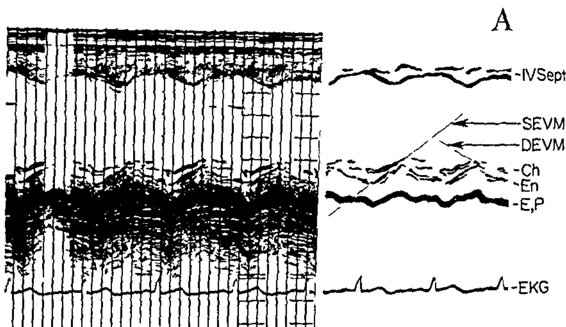


Fig 2A Echogram of a 13 year old boy with DMD showing simultaneous echoes of the interventricular septum *(IVsept)* chordae tendineae *(Ch)* left ventricular endocardium *(En)* and the epi pericardium *(E P)* Maximal systolic endocardial velocity *(SEVM)* and maximal diastolic endocardial velocity *(DEVM)* are derived from the slope of a tangent drawn to the steepest portion of the systolic or diastolic endocardial excursion

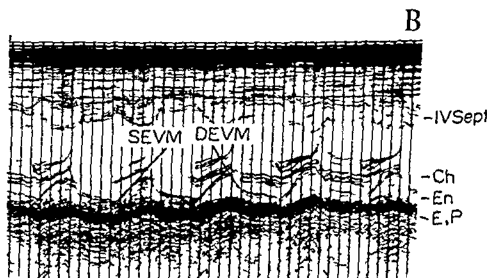


Fig 2B Note the diminished posterior left ventricular wall excursion (WALLE) and decreased maximal systolic endocardial velocity *(SEVM)* and maximal diastolic endocardial velocity *(DEVM)* of the DMD boy in Fig 2A compared to his BSA matched control subject

muscle and inferred a defective relaxation of myofibrillae possibly related to excess calcium content of mitochondria Kovick and co workers,[15] who initially described the subnormal echo DEVM in DMD subjects suggested this abnormality could manifest an interruption in the normal release and uptake of calcium within sarcoplasmic reticulum during contraction and relaxation Since the binding of calcium to sarcoplasmic reticulum has in fact been shown to be abnormal *in vitro* in preparations from human and animal dystrophic muscle[illegible] the subnormal WALLE and DEVM of early and late DMD could manifest an inherited disorder in Ca mediated contraction-relaxation

Echocardiogram abnormalities in late DMD (Table IV) In addition to the early changes discussed above the following disturbances now appear subnormal EF SEVM and Vcf These three changes unequivocally indicate impaired systolic performance of the heart in ejecting blood The underlying mechanisms could include three abnormalities known to be present in the late stages of DMD loss of myocardial muscle

cells accumulation of fibrous tissue in the myocardium and deconditioning A contribution by chest wall deformity is unlikely because a recent study by catheterization in non dystrophic patients with more advanced pectus excavatum than the present DMD boys showed no abnormality in supine contractile function

Possible clinical applications The present data have two possible applications

1 The lack of a statistically significant correlation between most echocardiographic indices and MMT (see Results section) suggests that DMD may progress at different rates in heart and in skeletal muscle Therefore the extent of heart involvement cannot be deduced by examining musculature of trunk and extremities Moreover cardiac physical examination chest x ray and ECG fail to reveal the progression of Duchenne heart disease because The ECG changes do not evolve with age chest deformity distorts the cardiac silhouette as in endocardial fibrosis deposition of connective tissue may partially counteract the tendency of the failing heart to dilate Consequently congestive failure tends to be unpredictable in DMD Echocardiography reveals the progressive changes in cardiac function during the life of the DMD child and should indicate when decompensation is imminent

2 Carriers of the DMD gene sometimes have mildly elevated SCPK and slight changes in muscle histology but identification of the carrier state is still uncertain Echocardiography showed impaired WALLE and DEVM in our youngest DMD boys whose MMT was virtually normal If as discussed above these changes reflect an inherited disorder of the contraction-relaxation process in muscle cells the echocardiogram may have some use in the detection of carriers of the DMD gene

Summary

Boys with Duchenne muscular dystrophy (DMD) rarely have clinical evidence of myocardial dysfunction during life Nevertheless congestive heart failure is a frequent terminal event and autopsy invariably shows dystrophic myocardial involvement Little is known regarding the progression of heart functional abnormalities in boys with DMD from birth to death Therefore we have examined the hearts of 18 DMD boys aged 4 to 15 years with the following non invasive methods cardiovascular physical examination electrocardiography chest x ray serum enzymes and echocardiography Control subjects were 25 normal boys matched to their DMD counterparts by age and by body surface area

The dystrophic patients were divided into early (N = 9) and late (N = 9) DMD according to manual muscle testing of skeletal muscles In early DMD six of 23 cardiac indices differed from control boys in the late stage an additional five indices became abnormal

Early DMD was characterized by these abnormalities tachycardia large ECG R/S ratio in V_1 augmented q wave voltages in Leads I II and V_5 of the ECG diminished contractile excursion of the left ventricular posterior wall (LVPW) and interventricular septum and decreased rate of relaxation of the LVPW

In late DMD additional cardiac abnormalities appeared enlarged heart volume by x ray reduced cardiac ejection fraction diminished change in left ventricular diameter from diastole to systole reduced maximal systolic endocardial velocity and decreased rate of circumferential fiber shortening as detected in the echocardiogram

Most of the cardiac abnormalities were revealed only by echocardiography which is thus shown to be a sensitive method for monitoring the progression of cardiac dystrophy during the life span of the DMD child

The authors are indebted to Drs Daniel Rudman Ellen Fuller Donald Nutter and Michael Kutner for their critical review of the manuscript

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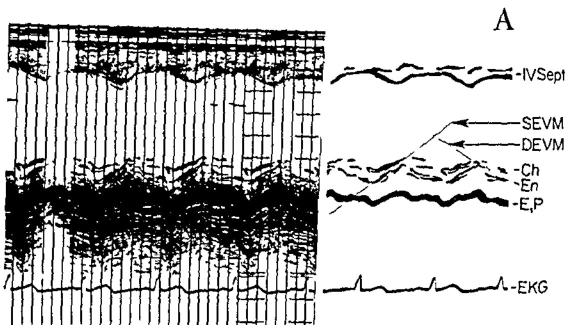


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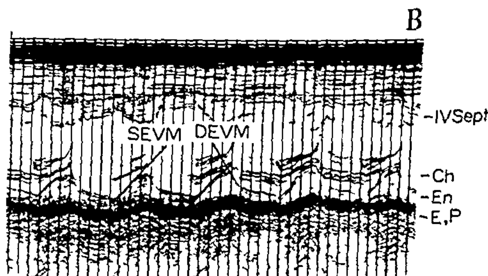


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Ondine s Curse Hemodynamic response to diaphragm pacing (electrophrenic respiration)

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Lawrence S Cohen M D
David Sheps M D
Steven Wolfson M D
William W L Glenn M D
New Haven Conn

Alveolar hypoventilation secondary to abnormal central nervous system control of respiration is an uncommon pathological condition Severinghaus and Mitchell who reported three patients believed to have sustained damage to the medullary carbon dioxide chemoreceptors as the result of neurosurgical procedures were the first to apply the name Ondine s Curse to this syndrome

Sarnoff and collaborators 25 years ago applied temporarily artificial respiration to several patients with ventilatory insufficiency secondary to bulbar poliomyelitis The technique of artificial respiration consisted of electrical stimulation of the phrenic nerve they termed this technique electrophrenic respiration (EPR) Long term stimulation of the phrenic nerve became possible with the successful development in our clinic of a cardiac pacemaker powered by a radiofrequency transmitter [5]

Electrophrenic respiration or as we have preferred to call it diaphragm pacing [3] has been investigated at Yale University School of Medicine since 1963 and it has been applied uccessfully to patients since 1966 This report presents the hemodynamic changes produced by diaphragm pacing in a selected series of patients with Ondine s Curse (Alveolar Hypoventilation)

Materials and methods

Eight patients with Ondine s Curse were studied following implantation of a radiofrequency electrophrenic respirator

Table I gives the clinical profile of these eight patients There were six males and two females Their ages ranged from 37 to 54 years with a mean of 49 years The presenting symptoms were congestive heart failure in eight patients somnolence in seven lethargy in three polycythemia in three and headaches in one patient Two of the patients were moderately obese On the electrocardiogram there were three instances of right bundle branch block two of right ventricular hypertrophy two of right axis deviation and two of right atrial hypertrophy Only two of the eight patients displayed a normal electrocardiographic pattern

The chest x ray was normal in only one patient The others demonstrated a variety of abnormal radiological findings Right ventricular enlargement dilatation of the pulmonary artery generalized cardiomegaly and pulmonary vascular changes compatible with pulmonary hypertension were seen alone or in combination

The probable etiology of this syndrome in these eight patients was primary hypoventilation in three electroshock therapy in two and in one

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PROTOCOL

REST BREATHING ROOM AIR

↓

EPR (diaphragm pacing) FOR 10 MINUTES

↓

REST BREATHING ROOM AIR FOR 10 MINUTES

↓

100% OXYGEN INHALATION FOR 10 MINUTES

↓

EPR PLUS OXYGEN FOR 10 MINUTES

Fig. 1. Pulmonary and systemic arterial pressures, systemic arterial blood gases, and saturation and cardiac output were obtained during each period. *EPR* = electrophrenic respiration alias diaphragm pacing.

Data were analyzed for significance of changes by the paired Student t test.

Results

Pulmonary artery pressure. There was a fall in mean pulmonary artery pressure on diaphragm pacing from 30 mm Hg at rest to 25 mm Hg ($p < 0.01$) (Fig. 2). The decrease was most prominent in cases with pulmonary hypertension. Administration of 100% oxygen by inhalation did not significantly affect mean pulmonary artery pressure and oxygen inhalation plus pacing did not decrease mean pulmonary artery pressure further than did pacing alone. There was no significant effect of 100 per cent oxygen by inhalation on pulmonary vascular resistance in these patients.

There was a similar fall in systolic pulmonary artery pressure on pacing from 44 mm Hg at rest to 35 mm Hg ($p < 0.02$) (Fig. 3). Oxygen inhalation did not significantly change the peak systolic pressure and pacing plus oxygen inhalation lowered the systolic pulmonary artery pressure to 33 mm Hg. Mean pulmonary capillary wedge pressure (Table II) averaged 15 mm Hg at rest and decreased to 12 mm Hg with pacing, to 14 mm Hg with oxygen inhalation and to 12 mm Hg oxygen plus pacing. This change was not statistically significant. Arteriolar vascular resistance (Table II) was calculated in only five of the eight patients and in these the resting average of 289 dyne/sec/cm^{-5} fell to 203 dyne/sec/cm^{-5} with pacing ($p < 0.05$) and to 229 dyne/sec/cm^{-5} with pacing plus oxygen inhalation ($p < 0.05$).

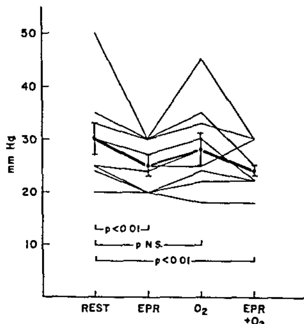


Fig. 2. Individual patient values and group means ± standard error of the mean for mean pulmonary artery pressure in eight patients with central hypoventilation syndrome during rest, EPR (diaphragm pacemaking), with O (oxygen inhalation), and with EPR + O (diaphragm pacemaking plus oxygen inhalation).

Table II. Hemodynamic profile of patients with Ondine's Curse

	No. of patients	*Rest*	*EPR*	*O*	*EPR + O*
CO†	5	4.15±0.07	3.93±0.1[illegible]	3.83±0.28	3.83±0.44
SAP	8	137±4	13[illegible]±5	141±5	130±5
DAP	8	77±4	75±4	70±9	74±4
PCW	8	15±0.3	12±0.6	14±0.4	12±0.5
PAVR	5	289±15	203±30	29[illegible]±42	229±54

All measurements are expressed as group means ± standard error.
*p < 0.05 paired t test compared with control measurements.
†Abbreviations: CO = cardiac output (expressed as liters per minute); DAP = diastolic aortic pressure (in mm Hg); EPR = electrophrenic respiration; EPR + O = electrophrenic respiration plus 100 per cent oxygen inhalation; O = 100 per cent oxygen inhalation; PAVR = pulmonary arteriolar vascular resistance (in dynes/sec/cm.$^{-5}$); PCW = pulmonary capillary wedge pressure (in mm Hg); SAP = systolic aortic pressure (in mm Hg).

Aortic pressure. Recorded during the four states, aortic pressure showed a minimal but statistically significant fall in systolic pressure with pacing and with pacing plus oxygen inhalation. Diastolic pressure and heart rate did not

Table I Clinical profile of eight patients with Ondine's Curse

YNHH Unit No	Sex	Age	Symptoms	Electrocardiogram	Chest x ray	Probable etiology
1 E D 78 55 08	F	54	Somnolence Lethargy CHF Polycythemia	RVH	Enlargement of right ventricle	Primary hypoventilation
2 S F 82 11 00	M	47	Somnolence Lethargy CHF	Normal	Normal	Electroshock therapy 3 mor hs previously
3 A D 80 83 22	M	54	Lethargy	RBBB RAD	Enlargement of pulmonary artery	Head trauma 10 years previously
4 M S 84 20 18	F	47	Somnolence CHF Polycythemia	RAH RVH	Enlargement of pulmonary artery and right ventricle	Viral encephalitis 38 years previously
5 J F 85 85 11	M	50	Somnolence CHF	Normal	Generalized cardiomegaly and enlargement of pulmonary artery	Poliomyelitis 40 years previously
6 W R 86 59 19	M	53	Somnolence CHF Polycythemia	RAH RAD	Generalized cardiomegaly and pulmonary vascular changes comparable with pulmonary hypertension	Primary hypoventilation
7 L T 86 01 13	M	37	Somnolence CHF Headaches	RBBB	Enlargement of right ventricle	Primary hypoventilation
8 R S 84 06-18	M	52	Somnolence CHF	RBBB	Enlargement of pulmonary artery	Electroshock therapy 1 year previously

Abbreviations CHF = congestive heart failure F = female M = male RAD = right axis deviation RAH = right atrial hypertrophy RBBB = right bundle branch block RVH = right ventricular hypertrophy

each of the remaining three trauma to the head viral encephalitis and poliomyelitis Studies on all patients clearly established that alveolar hypoventilation was on the basis of malfunction of central ventilatory control [15]

The patients underwent cardiac catheterization according to the protocol outlined in Fig 1 In each state listed pulmonary artery pulmonary wedge and systemic arterial pressures were measured through catheters placed in the pulmonary artery and central aorta To obtain pulmonary wedge pressure the catheter was passed from the pulmonary artery to the pulmonary capillary position and later withdrawn to its original place in the pulmonary artery The catheters were connected to Statham P23Db pressure transducers Reference point for pressure measurement was at the level of the patient's midchest in the supine position The pressure tracings were obtained using a multichannel recorder *

Cardiac output was measured by injecting indocyanine (green dye) into the pulmonary artery and sampling from the central aortic catheter The arterial blood traversed the densitometer that was connected with a recorder and integrator *

Arterial blood gases were measured in each state sequentially at rest after ten minutes of diaphragm pacing during a second period of rest after ten minutes of inhalation of two liters of 100 per cent oxygen and finally after ten minutes more of pacing

Artificial respiration was accomplished using a radiofrequency diaphragm pacemaker The characteristics of the pacemaker have been reported previously [4, 8, 13]

All hemodynamic measurements were done between five days and 18 months after the implantation of the electrophrenic respirator One patient underwent two separate studies one month and then one year after implantation

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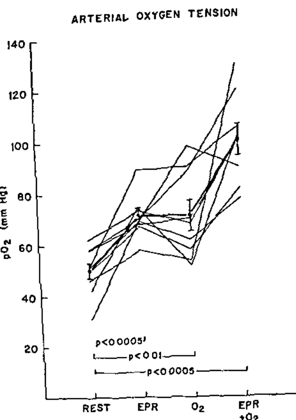


Fig 5 Individual patient values and group means ± standard error for arterial oxygen tension in eight patients with central hypoventilation syndrome

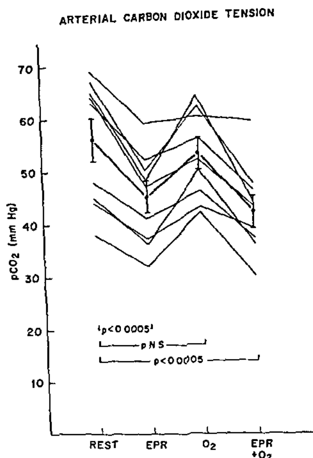


Fig 6 Individual patient values and group means ± standard error for arterial carbon dioxide tension in eight patients with central hypoventilation syndrome

dioxide tension increased arterial pH fell and systolic systemic pressure rose though insignificantly Finally when oxygen inhalation and pacing were used together the changes in all measured parameters were similar to those observed with pacing alone

It is evident that the patients in our series had pulmonary hypertension at rest and their pulmonary artery pressure diminished concomitant with the correction accomplished by pacing of hypoxemia hypercapnea and acidosis In the presence of chronic hypoxic pulmonary disease there is evidence of pulmonary vasoconstriction [11] Jameson [8] postulated that hypoxemia leads to vasoconstriction in the pulmonary pre capillary capillary and post capillary beds When hypoxemia alone was corrected in our patients the pulmonary artery pressure did not decrease suggesting that there must be factors other than hypoxemia contributing to pulmonary hypertension Von Euler and Liljestrand found that an increase in carbon dioxide tension raises the pulmonary artery pressure Liljestrand later attributed such elevation of pressure to an increase in hydrogen ion concentration Bergofsky and colleagues demonstrated that changes in pH influence vasoconstriction in the pulmonary vasculature

Since the correction of hypercarbia could only be accomplished by the use of diaphragm pacing we cannot distinguish between the effect on the pulmonary artery pressure of lowering the carbon dioxide tension or of raising the pH Calculated pulmonary arteriolar vascular resistance decreased only on pacing The mechanism for this was improvement in ventilation due to aeration of unventilated alveoli resulting in correction of hypoxemia hypercapnea and acidosis in addition there may have been an improvement in ventilation perfusion ratio in previously hypoven

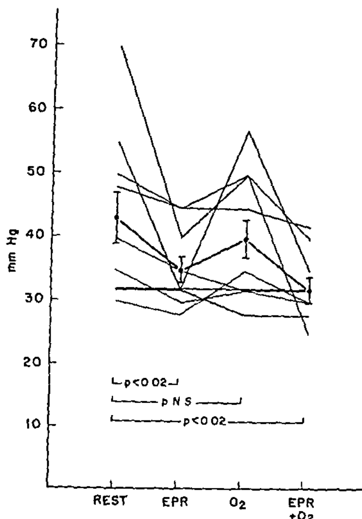


Fig 3 Individual patient values and group means ± standard error of the mean for systolic pulmonary artery pressure in eight patients with central hypoventilation syndrome during the four states Rest EPR (diaphragm pacemaking) O_2 (oxygen inhalation) and EPR + 0 (diaphragm pacemaking plus oxygen inhalation)

show significant change on any intervention (Table II)

Cardiac output This remained unchanged during the four states in five of the patients in whom it was measured (Table II)

Arterial blood gases The arterial pH averaged 7 39 ± 0 01 mm Hg during rest, increasing to 7 46 ± 0 01 mm Hg during pacing (Fig 4) Oxygen inhalation also tended to normalize the pH giving a mean value of 7 41 ± 0 01 mm Hg Oxygen plus pacing changed the pH to an alkalotic level of 7 49 ± 0 01 mm Hg The arterial Po_2 averaged 50 mm Hg at rest increasing to 70 mm Hg ($p < 0\,0005$) with pacing (Fig 5) Oxygen inhalation alone yielded a mean tension of 70 mm Hg Pacing plus oxygen inhalation yielded an O_2 tension of 100 mm Hg Pacing significantly

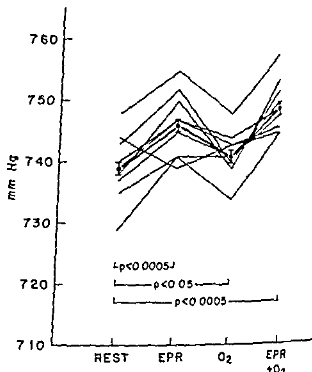


Fig 4 Individual patient values and group means ± standard error for arterial pH in eight patients with central hypoventilation syndrome

lowered the Pco_2 from a level of 55 mm Hg at rest to 44 mm Hg ($p < 0\,0005$) (Fig 6)

Discussion

Since the early studies of Sarnoff and coworkers [4] on temporary electrical stimulation of the phrenic nerve several studies from our clinic have shown that an effective exchange of oxygen and carbon dioxide can be achieved for prolonged periods using the radiofrequency diaphragm pacemaker [13] The present report documents the hemodynamics and blood gas alterations produced in eight patients with primary alveolar hypoventilation The clinical features manifested by most of these patients are similar to the one described by Richter and associates [15]

Pacing of these eight patients caused a fall in mean pulmonary arterial and systemic arterial pressure a fall in arterial carbon dioxide tension and a rise in arterial oxygen tension and pH Calculated pulmonary arteriolar vascular resistance also decreased with pacing When oxygen inhalation was used alone arterial oxygen tension rose but mean pulmonary artery pressure and calculated pulmonary arteriolar vascular resistance remained unchanged Arterial carbon

Measurement of the circulatory effects of dobutamine a new inotropic agent in patients following cardiac surgery

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The treatment of a patient with a low cardiac output is often disappointing and the approach to management controversial The use of pharmacological and physical agents to support and improve left ventricular function following low cardiac output states is at present a subject of considerable reappraisal Guidelines as to whether invasive methods such as balloon counterpulsation or medical pharmacological therapy should be employed have not been clearly defined In most hospitals medical management has the advantage that it is readily applicable With the introduction of peripheral vasodilators—salbutamol nitroprusside phentolamine for this clinical situation the role of inotropic agents—isoprenaline adrenaline dopamine has been criticized and become less clear To obviate some of the theoretical disadvantages of available inotropic agents new compounds have been synthesized

Dobutamine hydrochloride is a recently introduced cardioselective synthetic catecholamine with a structure similar to isoprenaline and dopamine Early studies with *this drug* revealed that it had potent inotropic activity but compared with other catecholamines it caused less increase in heart rate It had little effect on peripheral beta receptors and peripheral resistance was little altered As a result of this the reduction in diastolic coronary perfusion pressure seen with isoprenaline and the elevated systolic pressures frequently caused by adrenaline and dopamine do not occur with this drug

Unlike dopamine dobutamine does not rely for part of its action on the release of stored catecholamines which may be severely depleted after cardiopulmonary bypass when inotropic therapy is often indicated Animal studies have shown that the increase of cardiac output produced by dobutamine improves flow to the coronary and iliac beds but causes only a minimal change in renal blood flow Studies on myocardial infarction in dogs have demonstrated that dobutamine causes less increase in infarct size than other inotropic agents and suggest that this could be due to a combination of slower heart rate coronary vasodilation and maintenance of aortic diastolic coronary perfusion pressure Such studies suggest therefore that dobutamine is a potentially useful drug in the treatment of low output states

The object of this study was to compare the hemodynamic effects of dobutamine and isoprenaline in patients after cardiopulmonary bypass In addition we describe a new approach to intensive monitoring of the hemodynamic state

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tilated portions of the lung The present study indicates that patients with Ondine's Curse have a component reversible by the factors which lead to their pulmonary hypertension Thus, diaphragm pacing in such patients should effect substantial relief of cor pulmonale

Summary

The hemodynamic response to diaphragm pacing was studied in eight patients with Ondine s Curse It was shown that such pacing could lower the pulmonary artery pressure while correction of hypoxemia alone could not It was demonstrated that on pacing calculated pulmonary arteriolar resistance decreased and there was normalization of arterial blood gases The mechanism for these changes was improved alveolar ventilation

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Table I Hemodynamic values during dobutamine and isoprenaline infusion

Patient and amount infusion		*HR*		*BP*		*LAP*		*CI*		*SVI*		*PRI*		*SWI*		*% MA*	
		D	*I*	*D*	*I*	*D*	*I*	*D*	*I*	*D*	*I*	*D*	*I*	*D*	*I*	*D*	*I*
HB	o	80	80	126/62	126/6			2.5	2.5	31	31	33	33	35	35	100	100
	a	8	88	124/60	120/52			2 25	2 5	29	31	36	27	32	32	109	107
	b	86	100	136/60	128/54			2 55	3 3	30	33	33	24	35	36	12,	123
	c	91	110	140/60	10 /48			2.8	3 5	31	32	31	19	37	29	132	140
CB	o	105	100	10,/74	107/78	10	10	3.2	3 4	30	33	27	26	35	39	100	100
	a	106	102	107/75	110/78	9	10	3 3	3 6	31	35	26	25	36	42	110	100
	b	106	102	109/,8	112/,8	9	10	3 5	3 6	33	38		25	39	46	117	114
	c	119	121	110/81	122/ 5	7 5	9 5	4 7	5	39	42	19	18	48	52	135	126
MM	o	90	90	108/57	108/57	5	5	1 7	1 ,	19	19	44	44	19	19	100	100
	a	90	98	108/57	110/58	5	5	1 8	2 0	20	20	41	38	20	20	102	103
	b	95	100	116/58	103/54	5	4 5	2 1	2 1	22	21	3,	33	23	20	114	110
	c	90	118	127/59	111/59	4	5	2 1	2 4	23	20	39	32	26	21	126	129
AT	o	89	89	110/47	110/47	5	5	2 1	2 1	24	24	32	32	22	22	100	100
	b	93	98	110/47	117/54	3	3	2 5	7	27	28	28	8	26	29	107	10[illegible]
	c	107	124	126/50	97/47	3	3	2 9	3 2	2[illegible]	26	26	20	28	23	116	132
	d	120	137	119/47	115/46	3	3	3.2	3 5	2[illegible]	26	22	20	26	24	124	142
AH	o	5	75	120/70	1 0/ 0	8	8	2 8	2 8	37	37	31	31	43	43	100	100
	a	,6	90	126/,0	120/67	,	8	3	3 3	39	37	30	25	47	41	108	119
	b	84	93	130/64	122/60	8	7.5	3 8	3 6	44	39	23	23	52	43	119	125
	c	93	100	138/62	124/58	7 5	7	4 4	4.5	46	45	20	18	54	49	145	140
RR	o	102	102	94/57	94/57	8	8	2 3	2.3	3	23	30	30	22	27	100	100
	a	10	108	103/68	108/10	7.5	8	2 4	2 7	24	25	33	28	26	26	100	102
	b	109	111	111/68	111/66	7 5	7	2 5	2 8	24	25	33	29	27	28	106	10,
	c	130	136	130/77	103/57	8	8	3 3	3 3	25	24	29	27	32	24	123	121
MA	o	77	77	90/45	90/45	7 5	5	1 7	1 7	2	2	35	35	18	18	100	100
	b	101	100	10 /45	85/40	7	7 5	2 1	2 2	21	22	31	25	19	17	130	130
	c	103	122	110/45	90/40	7 5	7 5	2 3	2 4	2	20	29	24	20	16	136	133
	d	124	130	118/45	95/40	7.5	7	2 ,	2 6	20	20	28	22	19	16	152	145
BH	a	96	105	87/54	92/57	9	9	1 6	1.5	17	14	41	45	15	13	112	100
	b	96	111	84/50	104/62	9	8 5	1 [illegible]	2	18	16	36	38	15	19	140	148
	c	110	116	85/53	81/4,	8	9	2 3	2 3	23	20	28	25	20	16	168	172
AR	a	90	100	155/85	130/ 5	18	18	1 64	1 ,2	18	17	66	54	26	23	100	100
	b	98	115	150/80	140/75	14	15	1 90	2 20	19	19	54	44	27	25	110	111
AP	b	106	120	90/44	86/40	8	6	1 2	1.5	11	12	49	39	9	10	88	98
	c	115	128	104/48	102/48	6	7	1 8	2 1	15	16	37	31	14	14	120	118
JK	b	7	90	110/55	104/55			3 ,	3 7	45	41	21	19	45	40	97	100
	c	81	95	106/64	106/55			3 7	3 9	46	41	21	19	49	40	105	108
LM	b	83	8	130/62	109/58	8		2 ,	2 4	30	28	34	31	35	29	113	105
	c	88	91	130/60	120/60	7	8	2 7	2 6	31	29	31	31	36	3[illegible]	122	112
RMc	b	96	110	108/ 2	96/60	10	10	1 4	1 6	15	15	60	45	17	15	95	100
	c	104	118	114/ 0	104/62	10	9 5	1 6	1 8	16	15	53	42	19	16	127	136

a = 1.2 (01) b = 2 5 (02) = 5 (04) d = 10 (08) μg/Kg/min d but m ne (is prenaline)
HR = heart rat BP = blood pressure LAP = l ft atrial press re CI = card c d x SVI = st ok vol m index PRI = periph al res ta ce ind x SWI = st ke w rk ind x %MA = per ce t incre se in ma im l c lerat n D = dobutamin I = isoprenaline

Drug infusion The patients fell into two groups (1) those on no inotrope and (2) those patients who prior to the study had been stabilized on isoprenaline

1 *Patients on no drugs* After confirming that the patient was in a hemodynamically stable state (relatively constant cardiac output blood pressure left *and right atrial* pressure and heart rate for 1 hour) dobutamine 1 25 2 5 5 and 10 μg/Kg/min or isoprenaline 01 02 04 and 08

following cardiac surgery by which changes in blood flow and pressure may be more precisely evaluated

Subjects and methods

Patients Fourteen patients (10 men and four women) whose ages ranged from 21 to 56 years were studied All had undergone cardiopulmonary bypass surgery (repair of atrial septal defect, aortocoronary saphenous vein bypass grafting, and aortic valve replacement) within the preceding 24 hours Because of considerable hemodynamic variations in the immediate hours following cardiac surgery, these studies were performed when the patients were hemodynamically stable and in most cases this was between 16 to 22 hours after the cessation of bypass No patient had any mitral or aortic valve regurgitation

The nature of the investigation was explained and consent was obtained from the patients before the operation

All the patients were in sinus rhythm and with only one exception were being ventilated No other drugs or fluids were given during the investigation

Methods

Aortic flow measurement The use of the Williams Barefoot extractable aortic flow probe, produced a continuous display or aortic flow trace and its derived parameters[8] This flow probe is placed around the ascending aorta during surgery with its cable being exteriorized through a small incision to the right of the sternum The probe can be left in place for up to a week and when recording has been completed, by cutting an external snare the probe can be removed by gentle traction causing less discomfort to the patient than removal of a conventional drain The flow probe is connected to a Carolina 601D gated square wave flowmeter which gives a continuous display of cardiac output

The hemodynamic findings were obtained with equipment designed specifically for precise circulatory monitoring of the critically ill patient after cardiac surgery The Williams Barefoot extractable electromagnetic flow probe permits the continuous display of ascending aortic flow in the intensive care unit and has proved of great benefit in the assessment and management of patients after open heart surgery A more precise assessment of the effects of pharmacological and physical interventions is possible than with the conventional pressure and cardiac output measurements hitherto available Electromagnetic flow probe cardiac output measurements are more accurate than dilutional techniques especially in low output states[9] Values measured with the Williams Barefoot flow probe have been compared with rigid electromagnetic flow probes indocyanine green dilution cardiac output and thermodilution cardiac output Good correlation with all methods have been obtained A further advantage of the technique is that it is possible to derive other indices of aortic flow Peak aortic flow and maximal acceleration of flow,[10] and left ventricular power[11] have been used as indices of myocardial function, and may be readily obtained using this equipment

Other measurements Left and right atrial pressures and arterial pressure (radial or femoral artery) were measured using Statham 23Pd pressure recorded directly on to a Philips eight channel tape recorder and were analyzed downstream by the St Thomas' postoperative monitoring trolley This enables a continuous digital or meter display of cardiac output stroke volume stroke work, an index of peripheral resistance arterial pressure, left and right pressure and heart rate

In five patients a coronary sinus sampling line was left in place following surgery, and coronary sinus and arterial samples were taken and analyzed for lactate pyruvate and oxygen content

The hemodynamic variables were calculated from the basic data as follows

Cardiac Index (CI)
= Cardiac output/body surface area (L/min/M²)

Stroke Volume Index (SVI)
= Stroke Volume/body surface area (ml/min/M)

Stroke Work Index (SWI)
= SVI × (mean arterial pressure − right atrial pressure) × 0136 Gm m/M²

Systemic vascular resistance Index (SVRI) =

$$\frac{\text{(mean arterial pressure − right atrial pressure)}}{\text{Cardiac Index}}$$

mm Hg/L/min/M

The flow trace was passed through a differentiator and the first differential maximal acceleration of flow was measured The percentage change was calculated using either the resting or initial stable isoprenaline value as control

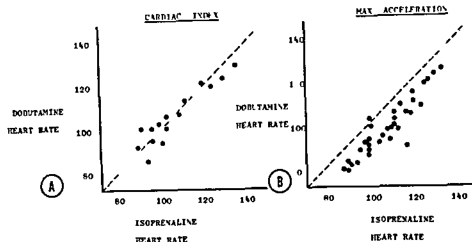


Fig 2 A comparison of the chronotropic effects of isoprenaline and dobutamine The heart rates produced by both drugs to achieve the same cardiac index *(a)* and maximal acceleration *(b)* in the 14 cases studied are plotted

$p < 01$ at the highest dose) Both drugs lead to a fall in peripheral resistance but this was more marked with isoprenaline

All patients remained in sinus rhythm during the infusions in two patients there was a slight increase in ventricular extrasystoles but some ventricular extrasystoles were evident during the control period The increase was small (two to five ventricular ectopics per minute) no infusion was stopped because of the development of dys rhythmias and there were no changes in ST segments or T waves which were monitored throughout in the investigation

In the five cases where simultaneous arterial and coronary sinus blood samples were taken there appears to be little difference in the meta bolic effects of both drugs (Table II) Compared to control levels there was no difference in A V oxygen content difference and both drugs appeared to reduce the lactate and pyruvate uptake of the myocardium There thus appears to be little benefit in myocardial economy from dobutamine when compared with isoprenaline in these patients

Discussion

Currently many drugs are advocated in the treatment of low cardiac output states after cardiac surgery Dobutamine in the present study has been shown to have an equi potent inotropic effect to isoprenaline with a reduced chronotropic and peripheral vascular action The changes in maximal acceleration and stroke work at a constant left atrial pressure occurred at a lower heart rate with dobutamine than with isopren aline and the drug caused a small elevation in systolic blood pressure The studies described were performed at a time after surgery when a stable hemodynamic situation had been achieved This precaution minimizes uncontrollable changes in the circulatory state which often occur in the immediate post bypass period i e such variables as fluctuations in the myocardial contractile state elimination of anesthetic agents employment of analgesic agents and vari able changes in fluid volume Rastelli and Kirk lin [2] have shown depressed cardiac function for 2 to 3 days following cardiac surgery and it seems likely that our results can be extrapolated back to the immediate postoperative period with the advantage that any changes observed in the hemodynamic state were probably induced by the drug

The cardiovascular effects of dobutamine which have been found in this study are not necessarily beneficial The cardiac output in patients after cardiac pulmonary bypass would appear to be relatively more dependent on heart rate than stroke volume Stroke volume is increased only slightly by inotropic agents [13, 14] and our results confirm that observation Since dobutamine has less chronotropic effect than isoprenaline the cardiac output for a given inotropic dose will be less

The second observed effect of dobutamine was that it provoked a modest elevation of arterial

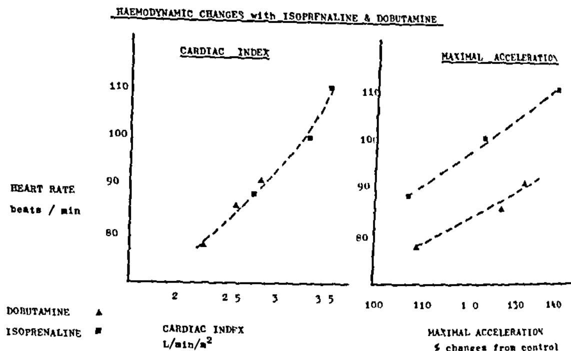


Fig 1 The hemodynamic changes in one patient (H B) during isoprenaline and dobutamine infusions changes in cardiac index and maximum percentage change from control in acceleration for a given heart rate are compared

µg/Kg /min were given each dose level for 7 to 10 minutes, starting with either drug in a random order with a 1 hour equilibrium interval between the different drug infusions The dose range was judged from previous reports to be the concentration of the drugs producing identical increments in cardiac output in patients studied during cardiac catheterization[4]

2 *Patients on isoprenaline* These patients were similarly confirmed to be stable, the isoprenaline dose was then doubled for 10 minutes and was then returned to the control level Once restabilized the patient was switched to dobutamine at 125 times the dose of isoprenaline for 10 to 20 minutes the dose was then doubled for 10 minutes The patient was then placed back onto the initial isoprenaline dose allowed to stabilize again, the dose was doubled for 10 minutes Either the isoprenaline data before or after the dobutamine infusion was analyzed, in a random order

Results

In both groups of patients in the dose levels chosen, dobutamine appeared to produce an equipotent inotropic effect when compared with isoprenaline Detailed results of the investigation are given in Table I

Both drugs produced a dose dependent increase in myocardial performance as measured by maximum acceleration of aortic flow and stroke work (left atrial pressure changed little during the infusions) Though both drugs caused an increase in heart rate dobutamine produced its improvement in inotropic action as measured by these two indices at a heart rate 10 to 15 per cent lower than isoprenaline (Figs 1 and 2)

The stroke volume was only slightly altered by increasing doses of both drugs (12 5 per cent and 13 9 per cent increase with the highest doses of dobutamine and isoprenaline respectively) As a result of this in these patients following open heart surgery, cardiac output is very dependent upon heart rate and thus any difference in chronotropic activity between the two drugs would not be revealed by a measurement of cardiac output alone Figs 1 and 2 show that the increase in cardiac index with dobutamine and isoprenaline was achieved at almost identical heart rates

The effects of the drugs upon blood pressure differed considerably Isoprenaline caused little change in systolic pressure but a fall in diastolic pressure (mean diastolic pressure fall at the highest dose was [3 ± 1 5 mm Hg $p < 0.$]) in contrast dobutamine maintained diastolic pressure at control levels and there was a moderate rise in systolic pressure (15 7 ± 2 9 mm Hg

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Table II Myocardial metabolism during infusions

Patient initials and drug	Arterial lactate*	% extraction†	Arterial pyruvate	% extraction†	A VO₂ difference
M M					
Control	96	−23	0 109	−8	6 9
Isoprenaline	1 00	0	0 105	3 8	4 2
Dobutamine	1 08	27	0 098	−4 5	6 5
A H					
Control	1 53	11	0 153	1 1	7 2
Isoprenaline	1 48	−7 0	0 138	−8 7	8 2
Dobutamine	1 57	10 8	0 136	8 0	9 9
R R					
Control	1 14	14	0 159	3 0	5 2
Isoprenaline	1 42	−4 9	0 169	−4 0	4 6
Dobutamine	1 28	−9 4	0 152	5 0	4 4
M A					
Control	69	10	0 092	7 6	10 3
Isoprenaline	79	−8 8	0 077	−18	9 2
Dobutamine	69	10	0 095	−39	7 4
L M					
Isoprenaline	5 14	6 8	0 413	3 8	
Dobutamine	5 17	−0 9	0 413	−4 6	

Lactate and pyruvate values are in micromoles/liter

$$\dagger \text{ extraction} = \frac{\text{coronary sinus conc} - \text{arterial conc}}{\text{arterial conc}} \times 100$$

pressure In low output states augmentation of aortic flow is more important than maintenance of a high arterial pressure provided that perfusion of vital organs does not fall below a critical value If the perfusion pressure to the coronary renal and cerebral arteries is adequate then further elevation of arterial pressure may be to the detriment of forward flow from the compromised left ventricle[15] Pressure work has greater metabolic requirements than volume work[16] It would appear that elevation of blood pressure is undesirable, especially if brought about by constriction of arterioles in vital organs Analysis of our measurements in the myocardial A V differences for oxygen lactate and pyruvate revealed that similar changes were caused by dobutamine and isoprenaline The results could be attributed to both an increase in coronary blood flow and substrate utilization by dobutamine or to identical changes in these variables with both drugs

Dobutamine appears to have little if any advantage over isoprenaline in patients who have undergone cardiac surgery, but our results should not be interpreted as necessarily applying to other clinical situations in which the cardiac output is reduced, in particular gram negative septicemia and myocardial infarction There is evidence to suggest that after experimental myocardial infarction in dogs, dobutamine causes less ischemic injury than isoprenaline for the same change in myocardial function[6,7] This was attributed to the absence of diastolic hypotension and reduced chronotropic action The incidence of dysrhythmias was also less than with isoprenaline Thus in the assessment of the utility or the appropriate use of a particular inotropic agent it may be necessary to define precisely the clinical circumstances

Summary

The use of an extractable aortic electromagnetic flow probe to provide a continuous on line display of ascending aortic flow and cardiac output following open heart surgery is described Utilizing this equipment, the hemodynamic actions of dobutamine and isoprenaline are compared in 14 patients immediately following cardiac surgery The study confirmed an inotropic action produced by dobutamine at a heart rate 10 to 15 per cent lower than isoprenaline with less peripheral vascular action Arterial and coronary sinus blood analyses revealed little difference in the myocardial metabolic actions of either drug Because inotropic drugs produce only relatively small increases in stroke volume in this group of patients, the rise in cardiac output caused by these agents is more dependent on the effects upon heart rate rather than improved myocardial contractile state and consequently dobutamine has little advantage over isoprenaline in this situation

We would like to thank Mrs Fiona Baile for her expert secretarial assistance We also acknowledge the cooperation of the nursing staff of the intensive care unit at St Thomas Hospital and Eli Lilly Ltd United Kingdom for financial assistance Dr Lewis was supported by the New Zealand National Heart Foundation

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Table I

Observations from the KCG
Duration of left ventricular thrust at K and K
Duration of isovolumic contraction at K and K
Duration of ejection retraction at K and K
Observations from the carotid pulse tracing
Shudder waves on the anacrotic limb
Time to peak percussion wave
Time to peak tidal wave
Character of the dicrotic notch
Left ventricular ejection time (LVET)

also had a standard kinetocardiogram (KCG) and carotid pulse tracing recorded within 48 hours of catheterization The technique of recording the KCG has previously been described[3,5] The apparatus consists of a flexible metal bellows suspended from a fixed position over the chest and having on one side a probe with a diameter of 7 mm that is fixed to the precordium in similar positions as the standard leads of an electrocardiogram The open end of the bellows is connected to a pressure transducer (Statham PL5A) and the absolute chest wall motion as sensed by the bellows during held mid expiration is transmitted to an Electronics for Medicine Recorder (Model DR 8) which gives a graphic record The resultant trace is the precordial movement usually palpable at the bedside Records were taken from the positions over the precordium corresponding to the electrocardiographic lead V (K) and V (K) The carotid pulse tracings were recorded by a glycerin pellet apparatus attached over the carotid artery with impulses transmitted by a transducer (Statham PL5A) and recorded simultaneously with the KCG Phonocardiograms were obtained with a Cambridge microphone and systolic time intervals measured by computer

A number of intervals were measured from the kinetocardiogram and carotid pulse tracing Table I demonstrates these

A typical recording is shown in Fig 1

The intervals are defined as follows Duration of isovolumic contraction (DURIVC) was measured beginning at 0 04 sec after the onset of the QRS and lasting until the onset of ejection as determined by the onset of carotid upstroke the duration of left ventricular thrust (DURLVT) was determined by drawing a baseline beginning at 0 04 sec after the onset of the QRS complex and measuring the duration of the intersect

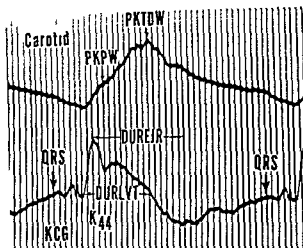


Fig 1 This figure presents the carotid pulse and the kinetocardiographic tracing from one of the patients with aortic stenosis The kinetocardiographic record was obtained on the K_{44} position on the chest wall which is comparable to the electrocardiographic V record but in the fourth intercostal space The onset of the QRS complexes of the electrocardiograph are indicated by an arrow The measurements made from these records include the time from the onset of ejection to the peak of the percussion wave *(PKPW)* the onset of ejection of carotid upstroke to the peak tidal wave *(PKTDW)* the direction of left ventricular ejection *(DURLVT)* taken from the kinetocardiographic record (see text) and the duration of ejection retraction *(DUREJR)* The vertical time lines represent 0 02 sec

during ejection retraction in the latter phase of systole The period was measured in hundredths of a second The duration of ejection retraction (DUREJR) was defined as the interval in hundredths of a second from the peak of forward motion or positive deflection of the kinetocardiogram to the end of systole and beginning of diastolic filling The ratio of the time intervals of left ventricular thrust to that of isovolumic contraction in the K_2 and K positions was utilized in addition to the single measurements From the simultaneously recorded carotid pulse tracing the time to peak percussion wave (PKPW) and the time to peak tidal wave (PKTDW) were identified as described by Tavel[8] The initial notching or rounding on the anacrotic limb was judged by visual inspection and defined as the peak percussion wave This point was occasionally difficult to define but strict criterion adherence allowed consistently reproducible data The peak tidal wave was defined as the plateau or secondary wave later in systole that occurred immediately prior to the dicrotic notch The ratio of these two values was also considered

Prediction of aortic valvular area and gradient by noninvasive techniques

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Valvular aortic stenosis is a surgically correctable disease when patient are identified and therapy instituted prior to irreversible decompensation or death Cardiac catheterization has been extensively utilized to evaluate patients with aortic stenosis and the findings of a peak to peak transaortic valvular gradient of at least 50 mm Hg and/or a calculated aortic valvular area of 0 8 cm or less have generally been utilized as criteria for surgical intervention The diagnosis of aortic stenosis and general classification of the severity of the disease in these patients can usually be accomplished by clinical evaluation and bedside examination as has recently been emphasized by Eddleman and associates[1] Noninvasive diagnostic techniques and/or cardiac catheterization are often necessary to define those patients in need of surgical therapy The purpose of this paper is to describe a noninvasive system that allows highly significant recognition of the severity of this disease and identification of those in need of valvular replacement

Patient selection

Sixty two patients were involved in this study The criterion for selection was that these patients had cardiac catheterization at the University of Alabama Medical Center Hospital or the Birmingham Veteran's Administration Hospital Each patient was found to have isolated aortic valvular stenosis and none had evidence of aortic valvular insufficiency Those studied were divided into two groups The initial group consisted of 44 males and six females with an age range of 16 to 77 years and a mean of 51 years The peak aortic gradient ranged from 12 to 150 mm Hg while the valve area ranged from 0 32 cm to 2 7 cm with the mean for the group 0 96 cm After the initial patients were evaluated in a retrospective manner to derive formulae by which to calaculate aortic valvular area and gradient from noninvasive data, 12 additional patients were studied prospectively to test the formulae as derived These 12 represent the population available with all necessary data at the time of the study Ten of these 12 had aortic valvular area calculated and all 12 had peak transaortic valvular gradient measured Five of the ten patients had a valve area less than 0 8 cm[2] and five had valve area greater than 1 cm The valve gradients ranged from 20 to 125 mm Hg in these 12 patients varying in age from 21 to 67 years with a mean of 51 years

These 62 patients represent the total population available with isolated valvular aortic stenosis and complete data as needed for the study at the time of its conduction

Measurements and methods

Each patient involved in the study had undergone right retrograde or transseptal left heart catheterization with Fick cardiac output determination and peak transaortic valvular gradient measurement The valve areas were calculated by the method of Gorlin and Gorlin[2] Each patient

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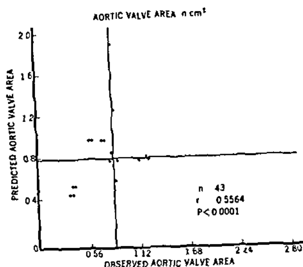


Fig 2 This figure presents the predicted aortic valve area plotted against the observed aortic valve area The grid has been placed across the record and it can be noted that those patients followed in the left upper quadrant or right lower quadrant were incorrectly identified

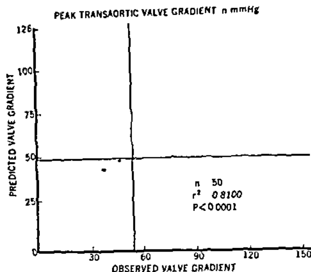


Fig 3 This figure presents the predicted valve gradient versus the observed valve gradient with the grid similarly imposed as in *Fig 2* It can be noted that the prediction of the peak transaortic gradient has a greater degree of accuracy than that predicted in the valve area

gradient by way of noninvasive techniques Initially however the noninvasive and catheterization data were examined together in order to correlate each variable s significance in relation to valve area Stepwise regression was used in this particular application

Table II demonstrates that the valve gradient determined from catheterization correlates more closely with the calculated valvular area than any of the variables considered singularly The individual correlation of the remaining variables is demonstrated in the order of their declining significance

The same variables were evaluated by the maximum r^2 method to determine the best model for aortic valve area prediction from the noninvasive techniques data The measured (catheter determined) transaortic valve gradient and calculated valve area were removed from the data prior to this application

The best of the models for valve area prediction consists of four variables The r^2 for the four component model is 0 5564 with $p < 0\,0001$ The variables are as follows The presence of calcium within the aortic valve (CA) vibration or shudder waves on the anacrotic limb of the carotid tracing (shudder) left ventricular hypertrophy (LVH) and the duration of ejection retraction in the K position (DUREJR K) Table III demonstrates the variables their individual value within the model as derived and the formula for predicting the valve area as determined by the method

For numerical purposes the presence of calcium within the valve was assigned the value of 1 if none was present 0 The duration of ejection retraction was measured in one hundredths of a second and entered as such in the formula The presence of left ventricular hypertrophy was given the score of 1 if present and 0 if absent and the presence of shudder waves was given a numerical score of 1 if present and 0 if absent

Fig 2 is a graphic plot of the predicted area on the vertical axis and the observed area on the horizontal axis for the initial group of fifty patients

A grid has been superimposed to demonstrate that only eight patients were incorrectly identified as to valve area greater or less than 0 8 cm² ± 1 cm One was predicted to be less than this limit as measured and seven were predicted to be greater As illustrated the r^2 is 0 5564 and $p < 0\,0001$ Thirty five of 43 patients or 82 per cent of the sample were correctly classified as to area of greater or less than 0 8 cm ± 1 cm² by utilizing the derived formula

The same data were employed to retrospectively predict peak transaortic gradient Comparison of the 22 variables by stepwise regression reveals that the single most significant variable in

Table II Individual variables and correlation coefficients in aortic valve area prediction

	Variable	*r*	*P*
1	Gradient	0 6736	0 0001
2	Calcification of the aortic valve	0 5603	0 0003
3	Shudder waves on the anacrotic limb of the carotid pulse tracing	0 4362	0 0037
4	Character of the dicrotic wave of the carotid pulse tracing	0 4028	0 0074
5	Left ventricular hypertrophy	0 3916	0 0092
6	Age of the patient	0 3133	0 0385
7	ST segment depression in Lead V of the ECG	0 2389	0 1190
8	Ratio of the duration of LV thrust to isovolumic contraction in K_1 of the KCG	0 2311	0 1372
9	Time to peak tidal wave from the carotid pulse tracing	0 2193	0 1542
10	Duration of the isovolumic contraction wave at K of the KCG	0 1723	0 2685
11	Ratio of the duration of LV thrust to the isovolumic contraction wave at K	0 1713	0 2715
12	Duration of ejection retraction at K	0 1692	0 2839
13	Duration of LV ejection time from the carotid tracing	0 1608	0 3163
14	Time to the peak of the percussion wave of the carotid tracing	0 1535	0 6733
15	Duration of the LV thurst at K_1 of the KCG	0 1449	0 6375
16	Ratio of the duration of the dicrotic wave to tidal wave duration of the carotid tracing	0 1377	0 6119
17	Duration of the isovolumic contractions wave at K of the KCG	0 0903	0 5764
18	Δ LV ejection time from the carotid pulse tracing	0 0804	0 6228
19	Duration of ejection retraction at K, of the KCG	0 0730	0 6505
20	Systolic blood pressure	0 0541	0 7333
21	Diastolic blood pressure	0 3607	0 8153
22	Duration of LV thrust at K	0 0008	0 9915

as a variable The dicrotic wave or notch was judged independently by at least two observers as being distinct slurred or indefinite and given a numerical coefficient for each that is distinct = 1 slurred = 2 and indefinite = 3 The duration of left ventricular ejection time (LVET) was measured from the carotid tracing by computer and compared to that predicted for heart rate (ΔLVET) and the presence of vibratory or shudder waves on the anacrotic limb of the carotid tracing was judged by visual inspection

Each patient also had cardiac fluoroscopy

Table III Four component model in aortic valve area prediction

Variable	*Probability > T*
Calcium within the valve (CA)	0 0009
Shudder waves on the anacrotic (Shudder) limb of the carotid pulse tracing	0 0076
Left ventricular hypertrophy (LVH)	0 0718
Duration of ejection (DUREJR K) Retraction at K of the KCG	0 1938
Formula	
Area = 209 22 – (CA) 72 21 – (Shudder) 44 48 – (LVH) 37 23 – (DUREJR K)1 38	

performed to determine the presence or absence of calcium in the aortic valve The brachial blood pressure was measured by pressure cuff Twelve lead electrocardiograms were evaluted by the criterion of Rombilt and Estes[9] for the presence or absence of left ventricular hypertrophy (LVH) This was entered as a variable as well as ST segment depression or T wave inversion alone in Leads V_5 or V_6 The age of the patient was also considered as a variable

Statistical analysis

Statistical analysis was performed by an IBM 370 155 system using a standard statistical program [10] This system allowed not only determination of a simple correlation coefficient but additionally, maximum r improvement analysis The maximum r improvement is a technique that approaches an all possible analysis It begins with the best one variable model with regard to r^2 and then adds the best remaining variables from the multivariant model to consider the effect of switching and finding those available Once the various combinations have been tried the variables are selected as to which improve the r^2 the most The principle distinction between this technique and the stepwise regression is that the latter always removes the least contributor to the prediction and enters the best single variable whereas r^2 improvement considers all combinations simultaneously The system yields a formula for determination of the desired value by weighing the contribution of each variable

Results

The data were evaluated in order to predict aortic valvular area and peak transaortic valvular

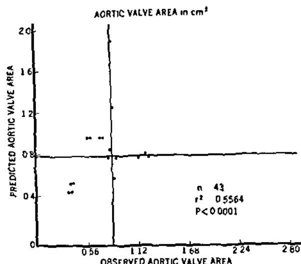


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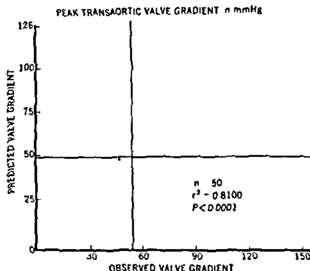


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For numerical purposes the presence of calcium within the valve was assigned the value of 1 if none was present 0 The duration of ejection retraction was measured in one hundredths of a second and entered as such in the formula The presence of left ventricular hypertrophy was given the score of 1 if present and 0 if absent and the presence of shudder waves was given a numerical score of 1 if present and 0 if absent

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The same data were employed to retrospectively predict peak transaortic gradient Comparison of the 22 variables by stepwise regression reveals that the single most significant variable in

Table IV Individual variables and correlation coefficients in aortic valve gradient prediction

	Variable	*r*	*P*
1	Valve area	0.6735	0.0001
2	Time to peak tidal wave	0.6549	0.0001
3	Left ventricular hypertrophy	0.5502	0.0001
4	Calcification of the aortic valve	0.5413	0.0002
5	Shudder waves on the anacrotic limb of the carotid tracing	0.4755	0.0008
6	Character of the dicrotic wave	0.4683	0.0010
7	ST wave depression in Lead V_6 of ECG	0.3803	0.0065
8	Duration of the ejection retraction in K of KCG	0.3722	0.0083
9	Left ventricular ejection time from the carotid pulse tracing	0.3393	0.0174
10	Δ left ventricular ejection time from the carotid pulse tracing	0.3335	0.0194
11	Time to peak percussion wave of the carotid pulse tracing	0.2894	0.0391
12	Ratio of dicrotic wave to tidal wave duration	0.2796	0.0[illegible]14
13	Ratio of LV thrust to isovolumic contraction wave of K	0.2684	0.0564
14	Systolic blood pressure	0.2668	0.0606
15	Duration of left ventricular thrust at K of the KCG	0.2511	0.0751
16	Diastolic blood pressure	0.2314	0.10[illegible]9
17	Duration of ejection retraction at K of the KCG	0.1924	0.1822
18	Age of the patient	0.1162	0.5729
19	Duration of LV thrust at the K	0.0792	0.5948
20	Duration of the isovolumic contraction wave at K	0.0633	0.6663
21	*Ratio of duration of* LV thrust to duration of the isovolumic contraction wave at K, of the KCG	0.0274	0.8461
22	Duration of the isovolumic contraction wave at K *of the KCG*	0.0013	0.9894

determining the gradient is valve area When the data from catheterization were removed the single predictors ranked as follows time to peak tidal wave of the carotid tracing LVH the presence of calcium within the valve shudder waves on the anacrotic limb of the carotid tracing, and in this fashion to the least sensitive predictor duration of isovolumic contraction at the K , position Table IV lists these individual variables and their respective correlation coefficients for gradient prediction

Prediction of aortic valvular gradient was performed by a similar procedure to prediction of aortic valve area A seven variable model gave the most sensitive and applicable determination The variables included in this are the presence of

Table V Seven component model in aortic valve gradient prediction

Variable	*Probability* > *T*
Left ventricular hypertrophy (LVH)	0.0001
Duration of ejection retraction (DUREJR K_{24}) at K of the KCG	0.0002
Calcium within the aortic valve (CA)	0.0011
Character of the dicrotic wave (DICROWAV)	0.00[illegible]1
Left ventricular ejection time (LVET)	0.0032
Time to peak percussion wave (TIMPKPW) of the carotid pulse tracing	0.0187
Duration of ejection retraction (DUREJR K) of K of the KCG	0.0335

Formula

Gradient = (−79.02) + (CA) 2[illegible].74 + (LVET) 0.2[illegible] + (LVH) 26.79 + (DUREJR K) 1.61 + (DICROWAV) 14.99 + (TIMPKPW) 0.78 − (DUREJR K) 0.75

calcium within the valve (CA) left ventricular hypertrophy (LVH), the duration of ejection retraction in the K , position (DUEJR K ,) the character of the dicrotic wave (DICWAV) the time to peak percussion wave (PKPW) duration of ejection retraction at the K_{44} position of the KCG (DUEJR K_{44}), and left ventricular ejection time (LVET) Table V lists these variables for gradient prediction and demonstrates the relative significance of each within this particular model A similar formula to that for valve area determination but applicable to peak transaortic valvular gradient was derived and is demonstrated

The numerical value for calcium within the valve was the same as previously shown while LVET was measured in msec and was entered as such in formula The remaining intervals were entered in hundredths of a second

Fig 3 demonstrates a plot of the predicted gradient along the vertical axis and the observed gradient along the horizontal axis for the initial group

A grid is again superimposed to correlate the predicted and observed gradient and to define the peak gradient of 50 mm Hg from predicted and observed determinations This demonstrates that only two patients with a gradient of greater than 50 mm were incorrectly identified and only five were predicted to have a gradient of greater than 50 mm Hg when the observed gradient was less than this significant point The r for the equation is 0.8100 and $p < 0.0001$ Forty three of 50

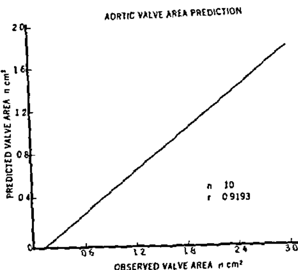


Fig 4 This figure presents a prospective series of patients using the multiple regression equation from the test series The predicted valve area is plotted against the observed areas The r value was 0 9193 and the significance has a p < 01

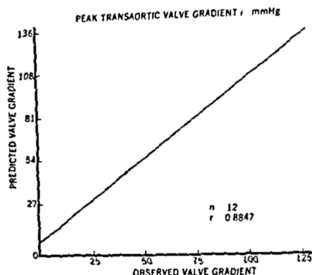


Fig 5 This figure presents the prospective series of patients using the multiple regression equation obtained from the test series The predicted valve gradient is plotted against the observed valve gradient The significance of this relationship revealed a p < 01

patients or 86 per cent of the sample were correctly classified as to peak gradient of greater or less than 50 mm Hg ± 2 mm Hg

The additional 12 patients were then studied in a prospective fashion by these derived formula in order to predict the aortic valvular area and peak transaortic valvular gradient while testing the formulae as derived Only ten of the 12 patients had aortic valvular area calculated by the method of Gorlin and these are demonstrated in the graph in Fig 4

All ten patients or 100 per cent of the sample were correctly categorized as to valve area by utilizing the derived formula illustrated in Table III The correlation coefficient for the prediction is 0 9193

The peak transaortic valvular gradient predictions were accurate within the group of twelve prospectively tested subjects These are shown in the graph in Fig 5

The correlation coefficient of 0 8847 is demonstrated for this evaluation in which ten of 12 patients or 83 per cent of the population were correctly identified by application of the derived formula in Table V

Discussion

Recent advances in aortic valvular surgery have enabled as good as a 90 to 95 per cent five year survival in those undergoing valve replacement [2] Much has been written about important signs and symptoms of the disease yet most significant contributions toward descriptors of the process have been cataloged from postmortem data as studies of Wood [13] Mitchell and colleagues [1] Grant [3] Braunwald and Ross [4] and Morrow and associates [17] The recent studies of Eddleman and co workers and Bonner and associates [8] have added insight to identification of significant disease in living beings but no prospective study encompassing only objectively obtained data has been reported prior to this writing This report demonstrates the validity of certain recognized associations and negates others in hemodynamically defined isolated aortic stenosis by examining these singularly and in combination It should be noted that these findings in all likelihood do not apply to infants and children with aortic stenosis

Aortic valve area is a sensitive and specific indicator of obstruction to left ventricular outflow Wood [3] required an area of 75 cm² or less before accepting the definition of significant stenosis The study of Frank and Ross[19] again illustrated the relationship of limited orifice size 70 cm² and a peak transvalvular pressure gradient of 50 mm Hg as criteria for significant obstruction in that 83 per cent of their patients with that degree of stenosis and without surgery died within a five year follow up period [19]

Aortic valvular calcification as detected by either chest x ray cardiac fluoroscopy or direct

examination is a common finding in severe valvular aortic obstruction Grant[15] discovered calcification in 65 per cent of stenosed aortic valves Wood[13] found it in 62 per cent of stenosed aortic valves Mitchell and associates[14] disclosed it in 80 per cent while Glancey and co workers[20] showed that 90 per cent of patients with aortic stenosis in their study had valve calcification The series of Eddleman and colleagues[1] indicated that 93 per cent of those with a gradient greater than 50 mm had calcification of the valve This study supports these previous observations in that 27 of 29 or 93 per cent of the population with an area of 80 cm ² or less and 40 of 43 or 93 per cent of those with a gradient of 50 mm or greater had aortic valvular calcification by fluoroscopy examination

Left ventricular hypertrophy (LVH) as deter mined by electrocardiographic criterion is a common finding in this disease Mitchell and associates[14] found that 84 per cent (74 of 121) of the patients in his study had left ventricular hypertrophy and Morrow and co workers[17] reported that 87 per cent of those with significant stenosis had LVH while 77 per cent had ST and T wave abnormalities in Leads V_5 and V_6 alone The presence of LVH as detected by a point score system was found in 27 of 43 or 63 per cent of those with a 50 mm or greater gradient and in 24 of 29 or 83 per cent of those with an area of 80 cm ² or less in our population Eddleman and colleagues[1] used a voltage method alone however, and found that only 71 per cent of those with a 50 mm or greater gradient had LVH ST and T wave alterations alone in the precordial leads were not found to be as sensitive in our study as had been previously reported

Prolonged left ventricular ejection item (LVET) as measured by systolic time intervals was described by Garrard and Weissler[21] as being compatible with aortic stenosis Bonner Sacks and Tavel[19] confirmed their observations and concluded that the LVET corrected for heart rate of 39 sec or less virtually ruled out significant aortic valvular obstruction while an LVET of 43 sec or greater was highly suggestive of severe stenosis The prolonged LVET as measured by computer methods was found to be a highly significant contributor to prediction of valvular gradient and area in our investigation by stepwise and multivariant analysis

Alterations of the anacrotic limb of the carotid artery tracing judged visually including shudder waves and a prolonged interval to the peak percussion wave, were also found to be reliable contributors to detection of outflow obstruction The latter is in variance to an earlier report of Lyle and associates[6] in examination of carotid artery slopes, yet this study considered only the visually determined changes rather than charac teristics measured by computer techniques

As the degree of aortic stenosis becomes more severe, the mechanics of valvular closure become altered A reduced or absent aortic valvular closure sound is a recognized finding in severe stenosis We visually judged the dicrotic notch of the carotid tracing as to whether it was distinctly present, slurred or indefinable and found that there is a highly significant correlation among stenosed valves and abnormal dicrotic notching in that only one of 43 patients with a gradient of 50 mm or greater and none of those with an aortic valve area of 80 cm ² or less had what was judged to be a normal dicrotic notch

The duration of ejection retraction as mea sured by the kinetocardiogram may be defined as another indicator of left ventricular ejection duration (Fig 1) Our data exhibits a close corre lation of both elevated gradient and reduced valvular area with prolonged ventricular contrac tion as this was included in predictive formulae for reduced aortic valvular area and elevated transvalvular gradient

The present investigation encompassed a broad spectrum of noninvasively obtainable data with the purpose in mind of identifying important signs in detection of severe aortic valvular steno sis The result has been to support some previously recognized positive correlates and to question others such as brachial blood pressure ST and T wave changes of the electrocardiogram as independent signs alone duration of measur able left ventricular thrust and the age of the patient The combined findings of calcification of the aortic valve left ventricular hypertrophy by point score electrocardiographic criterion abnor mal carotid artery tracings with shudder waves a poorly defined dicrotic notch by visual inspection and a prolonged left ventricular ejection may help to identify candidates for aortic valvular replacement

Summary

Sixty two patients with isolated aortic valvular stenosis were analyzed by a series of common noninvasive procedures and by cardiac catheteri

zation The data from 50 of these were evaluated in a retrospective fashion by multiple regression methods to determine significant objectively obtained predictors of aortic-left ventricular gradient and valvular area Formulae were derived from these analyses and an additional 12 patients were then studied prospectively to eval uate the validity of the predictive formulae

Forty three of 50 patients (86 per cent) were correctly identified as to a gradient of greater or less than 50 mm Hg in the initial group, and all those in the prospectively studied sample were correctly classified Thirty five of 43 patients (82 per cent) of those with valve area data in the first application were correctly classified as to valve area of greater or less than 0 8 cm² and all patients in the prospectively studied group were appropriately identified as to the same area

The combined application of the observations of calcification of the aortic valve shudder waves on the anacrotic limb prolonged time to peak of the percussion wave and alteration of the dicrotic notch of the carotid pulse tracing left ventricular hypertrophy by electrocardiogram and the altered duration of ventricular ejection time were reliable predictors of elevated aortic-left ventric ular gradient and decreased aortic valvular size

We are grateful to Dr Lloyd Hefner for his wise counsel and to Miss Lucile Romey Mrs Martha Crosman Mrs Etrulia Todd Mrs Linda Yeck, and Mrs Donna Fullerton for their secretarial assistance

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Histopathology of the conducting tissue of the heart in Chagas' myocarditis

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In 1909 Chagas first recognized that arrhythmias are the hallmark of the chronic myocarditis produced by the disease he discovered.[1] Electrocardiographic (ECG) correlations with this chronic myocarditis have subsequently stressed the high incidence of conduction disturbances (up to 87 per cent) with right bundle branch block (RBBB) predominating. RBBB was present in 48.3 per cent of 683 patients studies by Laranja and colleagues[3] in Brazil and in 55.7 per cent of 113 patients studies by Rosenbaum and Alvarez in Argentina.[4] Left anterior fascicular block (LAFB) is present in about the same frequency as RBBB and most often coexists.[5] Other ECG findings include atrioventricular block, premature beats, ST and T abnormalities, and other less important changes.[6] Left bundle branch block (LBBB) is rare, being present in only 2 per cent of the cases reported by Laranja and associates.[3]

Chagas disease is a potentially rich source of electrocardiographic and pathologic correlations due to the presence of characteristic myocardial lesions. In spite of this, few serial section studies of the atrioventricular conduction system are available, making very sketchy our knowledge of the type and distribution of the lesions responsible for the variety of conduction abnormalities characteristic of the disease. Torres and Duarte[7] and Andrade and Andrade[8] studied random sections through some portions of the conduction system in Chagas' myocarditis and found both inflammatory and fibrotic changes. Lev and co-workers[9] studied two cases of Wolf-Parkinson-White syndrome with Chagas disease. They observed chronic inflammation in the conduction system. In a patient with RBBB they also noted extensive fibrosis of the right bundle branch. Rosenbaum and associates[10] described histologic evidence for interruptive lesions in the RBB and in the anterior division of the LBB. In dogs infected with *T. cruzi* Anselmi and colleagues[11] noted that the delay in AV conduction correlated with fibrotic and inflammatory changes in the AV node and the bundle of His. Oliveira and co-workers[1] described a combination of inflammatory, degenerative, and fibrotic changes in a series of 30 cases of chronic Chagas myocarditis.

In this report we describe the pathologic abnormalities of 25 patients with Chagas myocarditis and correlate them with the electrocardiographic findings. A technique which employs complete serial sections mounted on continuous transparent plastic tape was utilized.

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Materials and methods

Twenty-five patients who died with Chagas myocarditis in Salvador, Bahia, Brazil, were selected for study. Complete autopsies were performed in all. Both clinical and pathologic features established the diagnosis of Chagas disease. These features are described in detail elsewhere. Complement fixation tests for *T. cruzi* infection (Guerreiro-Machado reaction) and/or xenodiagnosis were positive in all cases. Table I shows the main clinicopathologic and electrocar

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Table I. General data on 25 cases of Chagas' heart disease selected for clinicopathological study of the conducting system

Main ECG findings	No. of cases	Sex		Age (Yrs)			Heart weight (Gm)		
		M	F	Min	Aver	Max	Min	Aver	Max
RBBB + LAFB	15	9	6	21	38	64	220	562	800
RBBB + LPFB	2	2	–	20	–	44	450	–	670
LBBB	2	2	–	43	–	58	600	–	67[illegible]
Complete AV block	5	3	2	32	52	73	450	550	800
Absence of cardiac block*	1	1	–	–	17	–	–	410	–

*Acute Chagas' disease.
Note: Chronic diffuse myocarditis with interstitial fibrosis was present in all cases and its degree varied from moderate (+ +) to marked (+ + +).

diographic findings of the cases studied. The ECG tracings were analyzed according to the criteria of the New York Heart Association.[11]

One patient, case No. 1, died during the acute phase of Chagas' disease. He presented with a three week history of unilateral palpebral edema (Romaña's sign) and fever. *T. cruzi* were found in preparations from peripheral blood. He was living in an endemic area for Chagas' disease and had a positive Guerreiro-Machado reaction several months antemortem. Whether he had a relapse or a reinfection resulting in the acute disease is not known. All the other patients (cases No. 2 to 25) had chronic Chagas' myocarditis and died with progressive heart failure. In no case was there clinical or pathologic evidence of any other form of heart disease.

The hearts were opened in the usual manner and were fixed in 10 per cent formalin for three or four days. A block was cut from base of the atrial septum and upper third of the ventricular septum according to the methods described by Lev and associates for the study of the AV conducting system. The block was divided in two or three parts, embedded in paraffin, and cut serially. All sections (5 microns in thickness) were mounted on a continuous 35 or 70 mm. plastic tape according to the method described by Pickett and Sommer. Approximately two to six thousand sections were obtained from each block containing the AV conduction system. Sections were stained by the Masson's trichrome method. Available for study in all cases were the AV node, His bundle, and proximal portions of the bundle branches and Purkinje's fibers. The sinus atrial node (SAN) was studied in 12 cases following Hudson's technique but with serial sections being mounted on transparent plastic tape.

Representative sections taken from several areas of both atria and ventricles were also studied by conventional histologic methods.

Multiple random sections taken from posterior atrial walls (areas around the entrance of the inferior vena cava and in between the pulmonary veins) were utilized for the study of the intracardiac autonomous nervous ganglia.

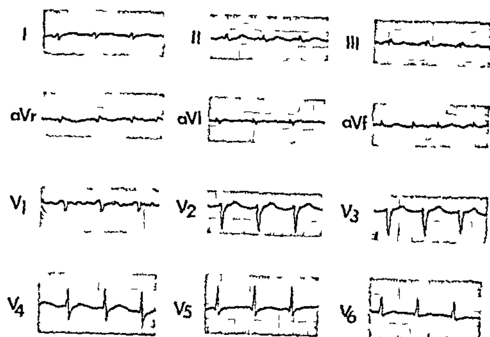
Results

Acute Chagas' myocarditis. Case 1. The pathologic findings were characterized by inflammatory changes throughout the conducting system. The conducting fibers were separated by a moderate degree of edema and diffuse mononuclear infiltrates. Histiocytes, lymphocytes, and plasma cells constituted the main inflammatory cells but small foci of polymorphonuclear infiltrates were also observed. Amastigote forms (multiplying forms of *T. cruzi*) were scattered throughout the AV conduction system. Vascular congestion was prominent. No necrosis, hemorrhage, calcification, or fibrosis was seen. Ruptured amastigote-containing myofibers were surrounded by inflammatory cells. Similar but more severe changes were seen in the contractile myocardium.

The ECG showed low voltage and ST and T abnormalities (Fig. 1). There were atrial fibrillation with a high ventricular response.

Chronic Chagas' myocarditis with RBBB and left anterior fascicular block. Fifteen cases can be described together because they all present essentially similar histopathologic findings. The ECG abnormalities were also essentially the same (Fig. 2). The different areas of the AV conduction system showed varying degrees of involvement and will be described separately.

AV node. Examination revealed a mild diffuse fibrosis with scattered foci of lymphocytes



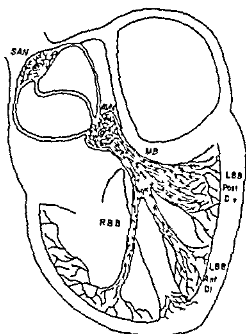
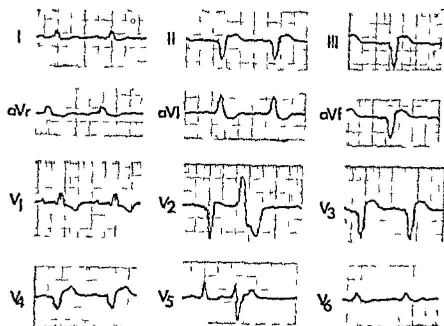


Fig 1 Seventeen year old male patient *Three week illness* Atrial fibrillation with high ventricular response



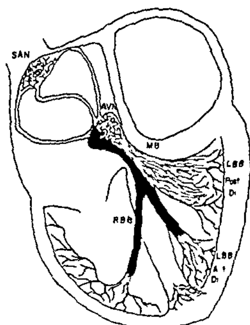


Fig 2 Twenty nine year old male patient *Seven month illness Right bundle branch block and left anterior* fascicular block

macrophages and a few plasma cells At the inferior (distal) portion of the node there were areas of fibrosis muscular atrophy and fatty infiltration These areas became more apparent in the penetrating *portion In two cases the nodal* artery showed intimal thickening as well as fibrosis and hyalinization of the media

His bundle Selective involvement of the right half of the His bundle was a *striking feature in* these cases (Fig 3) The left half showed minimal or no abnormalities Pathologic changes in the right half of the His bundle consisted of diffuse fibrosis focal lymphocytic *infiltration muscular* atrophy and mild fatty infiltration In addition there were vascular abnormalities characterized by *tortuous* dilated sclerosed thick *walled chan nels with a few atrophic myocardial* fibers among *them Often these abnormal* vessels were more numerous in the right side of the His bundle and partially replaced it Occasionally these abnor *mal vessels were seen* in the left half of the His bundle particularly in the region of the bifurca tion

Left bundle branch The proximal *2 5 to 3 cm*

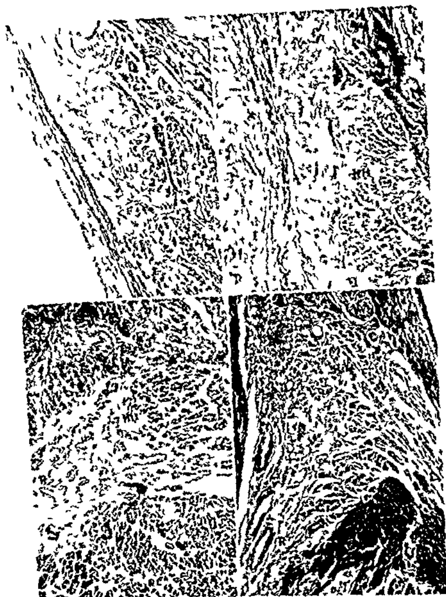


Fig 3 Four examples of the selective lesions affecting the right half of His bundle *Upper right* the penetrating portion of the His bundle already shows fibrosis and muscular atrophy at the right half *Upper left* while the left portion of the His bundle is preserved there is fibrosis atrophy and chronic inflammation involving the right half *Bottom right* a comparison can be made between the normal looking left half of the His bundle and its diffusely fibrotic right half *Bottom left* the lesions affecting the right half of the His bundle in this case are represented by vascular dilatation fatty infiltration atrophy of specific fibers and lymphocytic infiltration

of the left bundle was examined *Focal lesions* consisting mainly of fibrous replacement of myofibers were seen throughout the left bundle The anterior division was more severely involved In addition to fibrosis there were focal changes similar to those described above namely atrophy of myofibers chronic inflammation and small vessel changes

Right bundle branch Moderate to severe involvement of the right bundle branch was present in all 15 hearts The e changes were of a focal or segmental nature and were characterized primarily by fibrosis and atrophy and/or necrosis of conducting myofibers The vascular changes noted in the His bundle occasionally extended toward the proximal portions of the right bundle A few lymphocytes were scattered in between the fibers of the right bundle branch

Purkinje fibers The subendocardial Purkinje fibers were usually normal Rare foci of subendo

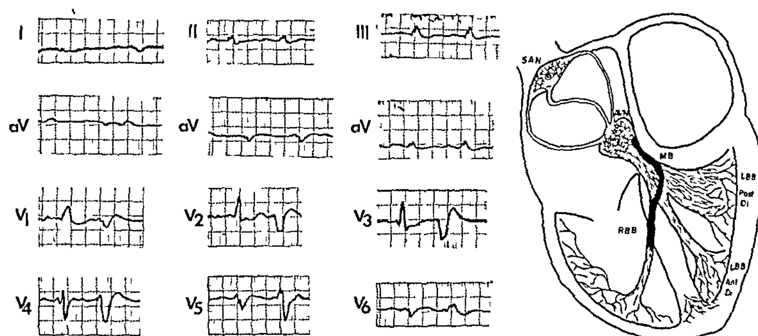


Fig 4 Forty one year old male patient Six month illness Right bundle branch block and *left posterior fascicular block*

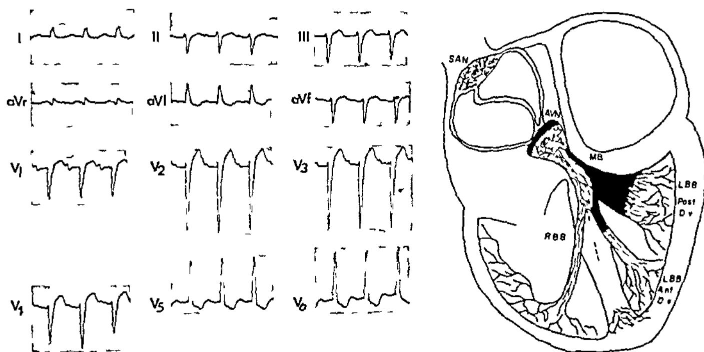


Fig 5 Fifty eight year old male patient Three year illness Complete left bundle branch block

cardial fibrosis occasionally replaced Purkinje fibers in the distal portions of the left bundle branch

Chronic Chagas myocarditis with RBBB and LPFB This pattern is exemplified by two cases in which there were moderate to severe fibrosis atrophy and vascular changes in the His bundle RBB and posterior division of the left bundle with total preservation of the anterior division (Fig 4)

Chronic Chagas myocarditis with complete LBBB Two cases had this electrocardiographic pattern In one case serial sections showed diffuse fibrosis extending from the AV node to the bundle branches with no selective involvement of the right half of the His bundle The short His bundle bifurcated early The left bundle branch was a distinct tract that came off the His bundle as a compact fascicle This is in contrast with the usual pattern in which fibers originate from the His bundle a few at a time over a considerable area This compact left bundle was completely

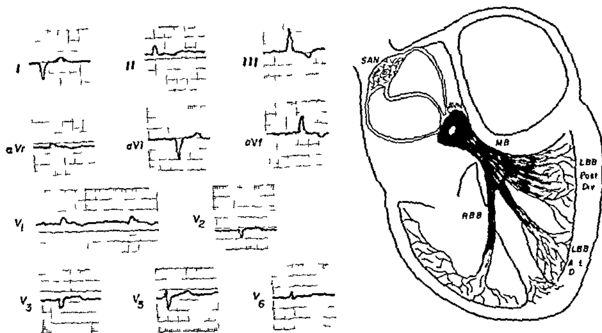


Fig 6 Forty-one year-old female patient Ten month illness Complete atrioventricular block.

interrupted by dense fibrosis and focal calcification in the proximity of the summit of the intraventricular septum The entire AV conduction system in this case showed very marked vascular changes consisting of tortuous channels with thickened and hyalinized walls and focal luminal stenosis The right bundle branch showed moderate focal fibrosis and atrophy with rare foci of chronic inflammation In the other case a diffuse atrophy was present in the entire LBB while the other parts of the AV system were preserved except for the anterior half portion of the AV node which was replaced by fibrosis (Fig 5)

Chronic Chagas myocarditis with complete (third degree) AV block Five cases showed this ECG change Lesions of fibrosis atrophy fatty infiltration vascular dilatation and thickening were diffusely distributed throughout the AV conduction system (Fig 6) In two cases the AV node the main bundle and the right bundle branch were more severely affected In one case the main lesions were localized in the distal portions of the bundle branches and consisted of sclerosis and atrophy

SA node Moderate to marked fibrous replacement of the specialized muscle fibers occurred in all cases, together with a slight to moderate degree of infiltration by lymphocytes plasmocytes and macrophages Sinus artery showed hypertrophy of the media and subendothelial fibrous thickening In one case this latter change was an outstanding one (Fig 7)

Intracardiac autonomic nervous ganglia Changes were present in all 12 cases studied The ganglia showed a considerable decrease in the number of nerve cells which appeared replaced by fibrosis and proliferation of peri ganglionic cells (satellitosis) Infiltration by mononuclear inflammatory cells occurred within and around the ganglia

No difference could be detected in the nature and degree of changes present in the ganglia taken from the right as compared to those from the left atrial wall

Purkinje fibers were frequently damaged by acute and chronic inflammation and fibrosis as were ordinary myocardial fibers

Discussion

Rosenbaum and associates[1] suggest on the bases of their and other investigators observations that the high incidence of RBBB and LAFB in chronic Chagas myocarditis is to be predicted in a panmyocarditis The right bundle branch is longer than and follows an intramyocardial course while the left bundle branch is shorter spreads over a large area and is primarily subendocardial Therefore Rosenbaum and associates predict that the evenly distributed random

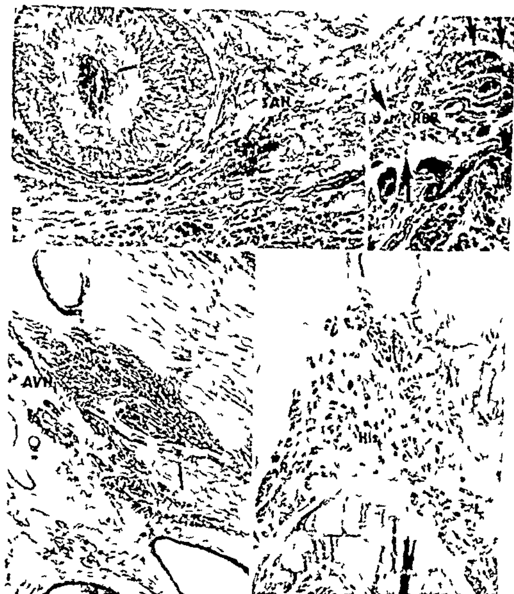


Fig 7 *Upper right* SA node showing considerable thickening of the nodal artery atrophy of fibers chronic inflammation and fatty change This patient presented sinus dysfunction and sudden death *Upper left* a subendocardial portion of the right bundle branch disclosing fibrosis and small vessel changes *Bottom right* considerable vascular ectasia is seen in the vicinity of the AV node These vascular alterations usually would proceed along to the His bundle and its branches *Bottom left* diffuse sclerosis vascular dilatation inflammation atrophy and fragmentation of specific muscular fibers can be observed in the His bundle and its branches From a case of complete AV block

lesions of a panmyocarditis would most likely cause interruption of the right bundle branch most often the left anterior division next in frequency and the left posterior division least often

Our findings demonstrate that the lesions of chronic Chagas myocarditis are not distributed randomly through the atrioventricular conduction system In the cases of chronic Chagas myocarditis that we have studied there is clearly a preferential distribution of the lesions within the conduction system The electrocardiographic findings reflect this distribution

In case No 11 with RBBB and LAFB there are only minimal inflammatory changes in the right bundle while the right side of the His bundle the AV node and the anterior division of the left bundle are the sites of fibrosis necrosis and atrophy of the conduction fibers This suggests that the disruption of the conduction to the RBB is occurring at some point proximal to it and supports the Sherf and James hypothesis[11] that longitudinal dissociation occurs within the fibers of the His bundle The inflammatory changes observed in the right bundle branch are unlikely to account for the RBBB pattern since it is known that RBBB does not occur in the acute states of Chagas myocarditis when the inflam

matory lesions predominate [3] In our own case No 1 of severe acute Chagas myocarditis which resulted in death of the patient conduction disturbances were absent in spite of massive inflammation and presence of intracellular parasites

This study offers an alternate explanation to the conduction disturbances characteristic of chronic Chagas myocarditis Careful examination of thousands of histologic serial sections of the atrioventricular conduction system unexpectedly revealed small focal strategically located lesions involving predominantly the right half of the His bundle the right bundle and the anterior division of the left bundle branch This distribution closely follows the known electrocardiographic evidence of conduction disturbances Selective involvement of the right half of the His bundle has been considered as a cause of RBBB by Corsi and colleagues [8] and this suggestion has been experimentally supported Such selective lesion has also been noted by Lev and co workers [6] in three cases of idiopathic myocarditis and by Oliveira and associates in chronic Chagas myocarditis

In particular the peculiar localization of the lesion to the right half of the His bundle was most striking Why should an inflammatory or degenerative lesion remain limited to one side of the His bundle? There does not seem to be any significant difference in the distribution of blood vessels [2] lymphatics [7] or nerves [5]

Changes in the intracardiac autonomic nervous system were present in all cases examined They did not correlate either in degree or location with the changes present in the conduction system However much remains to be learned about the relationships of the conduction system and the autonomic innervation of the heart

Lesions affecting the conduction system in chronic Chagas myocarditis are progressive Cases presenting with complete AV block show an end stage picture with diffuse fibrosis fatty infiltration and inflammation that differ from the simple sclero atrophy of distal branches described in cases not associated with Chagas disease [2]

Pathogenesis of the lesions found in the conducting system is rather difficult to explain Pathogenesis of Chagas myocarditis itself is still obscure

The polymorphism and variable combinations of the lesions are suggestive of a complex and multifactorial pathogenesis The basic lesion is inflammation However vascular and nervous factors probably play a role More data on the role of lymphatics and the autonomic nervous system of the heart seem necessary for the understanding of the pathogenesis of the changes affecting the conducting tissue of the heart in chronic Chagas myocarditis

Summary

The conducting tissue of the heart was studied in 25 human cases of Chagas myocarditis with a method which employs complete serial sections mounted on continuous transparent plastic tape The pathological changes were correlated with electrocardiographic findings

The inflammation of the acute phase of Chagas myocarditis as seen in one single case did not seem to interfere with conduction through the AV system

In chronic Chagas myocarditis the conducting tissue showed extensive and variable changes chronic inflammation fibrosis atrophy and fragmentation of specific fibers extreme dilatation and tortuosity of veins capillaries and lymphatics fatty infiltration and arterial medial and intimal fibrosis

A preferential involvement of the right bundle branch and the anterior fascicles of the left branch was observed and an excellent correlation with electrocardiographic abnormalities was found There was also evidence presented that bundle branch block may be caused by disease proximal to the bundle branches

Complete AV block seemed to be the final result of the progressive inflammatory and degenerative changes involving the conduction system in chronic Chagas myocarditis

Inflammation and fibrosis did also involve the sinoatrial node Purkinje fibers intracardiac nervous ganglia and the contractile myocardium

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Total effective compliance of the vascular bed in essential hypertension

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Capacitance vessels which affect the filling of the heart may play an important role in the control of cardiac output of hypertensive patients Most of the previous studies in hypertension were based on the estimation of pressure-volume relationships in segments of cutaneous veins and/or forearm vascular beds [3] However a quantitative evaluation of the role of capacitance vessels requires the determination of the over all pressure-volume relationship of the total systemic venous bed In animals such a determination is easy to obtain when the heart is stopped In humans a similar relationship between total blood volume and central venous pressure can be established when the heart is beating [4,5] In such a determination the elastic properties of the vascular bed cannot entirely explain the pressure changes in the central veins Secondary effects of blood volume changes on arterial hemodynamics and venous tone also contribute to variations in central venous pressure In this case the term effective compliance is used to describe the correlation

The purpose of the present study is to determine total effective compliance in permanent essential hypertensive patients and to evaluate the role of capacitance changes in the control of cardiac output in these subjects

Material and methods

Patients The study was performed in 31 men nine normotensive controls and 22 permanent essential hypertensive patients Permanent hypertensive patients were untreated or had discontinued their therapy at least 4 weeks before the study They were hospitalized for 6 days and placed on a diet containing 110 mEq sodium per day On the third day of hospitalization diastolic pressure was constantly equal to or above 90 mm Hg

Extensive investigations included blood and urinary electrolytes catecholamine determinations endogenous creatinine clearance and timed intravenous urography All patients were listed as essential hypertensives Clinical characteristics are indicated in Table I Mild to moderate left ventricular hypertrophy was observed in eight patients None had cardiac or neurologic involvement

The protocols were approved by INSERM (Institut National de la Santé et de la Recherche Médicale) Consent for investigations was obtained from the patients after a detailed description of the procedure

Hemodynamic parameters On the third day of hospitalization hemodynamic studies were per

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This study was supported by a gr[illegible]nt-in[illegible]d f[illegible]om th[illegible] In[illegible]titut de l[illegible] Santé et de la Recherch[illegible] Méd[illegible]al (INSERM Paris) th[illegible] Associat[illegible]on pour l'Utilisation du R[illegible]n Art[illegible]ficiel (AURA Paris) a[illegible]d the Délégation Général[illegible] à la Rech[illegible]r[illegible]he Scient[illegible]fique et Techn[illegible]q[illegible]e (DGRST)

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Table I Clinical characteristics

	Controls	*Hypertensives*
Number of patients	9	22
Age (years)	33 ± 4	37 ± 2
Weight (kg)	66 ± 4	76 ± 3†
Height (cm)	173 ± 2	175 ± 1
Body surface area (M^2)	1.78 ± 0.05	1.90 ± 0.03**

± 1 standard error of the mean
**p value < 0.01
†p value < 0.0?

Table II Hemodynamic parameters

	Controls	*Hypertensives*
Number of patients	9	22
SAP (mm Hg)	129 ± 3	184 ± 5
DAP (mm Hg)	76 ± 2	106 ± 3 *
MAP (mm Hg)	97 ± 2	134 ± 4 *
CVP (mm Hg)	4.2 ± 0.8	5.7 ± 0.4
CI (ml/min/M^2)	3747 ± 196	3356 ± 84
SI (ml/M^2)	51 ± 4	45 ± 3
HR (beats/sec)	76 ± 4	77 ± 2
TPR (dyne sec cm /M)	2110 ± 136	3170 ± 112**
TBV (ml/M)	2978 ± 118	2711 ± 50
TPV (ml/M)	1660 ± 57	1483 ± 33 *
CPBV (ml/M)	711 ± 36	667 ± 26
CPBV/TBV (%)	24.1 ± 1.3	24.4 ± 0.8

± 1 standard error of the mean
*p value < 0.05
**p value < 0.01
***p value < 0.001
Abbreviations SAP = systolic arterial pressure DAP = diastolic arterial pressure MAP = mean arterial pressure CVP = central venous pressure CI = cardiac index SI = stroke index HR = heart rate TPR = total peripheral resistance TBV = total blood volume TPV = total plasma volume CPBV = cardiopulmonary blood volume

formed after the patients had fasted overnight No premedication was administered Under local procaine anesthesia an antecubital vein and brachial artery were catheterized and the catheters were advanced into the right atrium and the aortic root immediately distal to the aortic valves respectively Central venous pressure was measured with a Statham strain gauge An imaginary line parallel to the experimental table and at one third of the distance between the anterior chest wall and the table was used as baseline for the gauge A large forearm vein was cannulated for infusion With the subject in the supine position cardiac output was measured at least

Table III Correlation coefficients of the relationships between effective vascular compliance and other clinical and hemodynamic variables in hypertensive patients

Correlation of effective compliance with	*r value†*
Age	−0.33
Weight	−0.10
Height	−0.14
BSA	−0.15
SAP‡	−0.57
DAP	−0.58 *
MAP	−0.62
CVP	−0.23
CI	−0.58
SI	−0.32
TPR	−0.21
CPBV	−0.45
TBV	0.03
CPBV/TBV	−0.58

*p value < 0.05
**p value < 0.01
†No correlation coefficient was significant in control subjects
‡See Table II for abbreviations

three times using Water s Cuvette and densitometer as previously described[9,10] Indocyanine green (5 mg) was introduced into the central venous catheter and flushed into the circulation in less than 0.5 sec With a constant rate pump blood was withdrawn from the arterial catheter through the densitometer Blood was reinfused The system was calibrated before each determination Curves were measured planimetrically Cardiac output was expressed in ml/min/M^2 thus correcting for body surface area Arterial pressure and central venous pressure were measured with a Siemens recorder Total peripheral resistance (TPR) was calculated according to the formula

$$TPR = MAP/CI \times 80$$
(dynes sec cm $^{-5}$/M^2)

where MAP was mean arterial pressure (mm Hg) and CI was cardiac index (ml/min/M^2)

Cardiopulmonary blood volume was defined as the volume between the right atrium and the tip of the arterial catheter It was calculated by the Stewart Hamilton method as follows CPBV (ml/M) = CI (ml/min/M^2) × MTT where *MTT* is the mean transit time in seconds from the right atrium to the tip of the arterial catheter The correction for the sampling system was

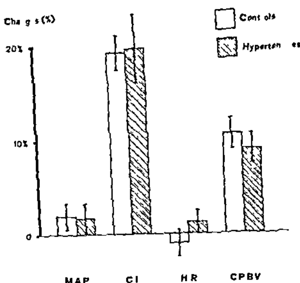


Fig 1 Changes in hemodynamic parameters before and after expansion in normotensive controls and hypertensive patients Basal absolute values are indicated in *Table II* *MAP* = mean arterial pressure *CI* = cardiac index *HR* = heart rate *CPBV* = cardiopulmonary blood volume

substracted from the observed time in calculating MTT

Before the hemodynamic study total blood and plasma volumes were measured in the recumbent position by the isotopic dilution method using radioiodinated albumin as previously described After withdrawal of a control sample 3 μc were injected Ten minutes later a sample was taken for radioactivity to be counted Blood volume was normalized for body surface area [1]

Effective vascular compliance The study was performed in the supine position with a room temperature between 23 and 25 C The procedure was a modification of that described by Echt and associates Effective compliance was determined during blood volume expansion using a dextran infusion In order to minimize secondary effects due to capillary filtration and delayed compliance the study was carried out in the shortest possible time Five hundred ml of 6 per cent dextram were infused within 4 minutes by a Sogreath MP 66 pump Cardiac output and cardiopulmonary blood volume were remeasured at the end of the infusion Central venous pressure was recorded during expansion and plotted against the volume (V) changes The pressure-volume relationship was practically linear

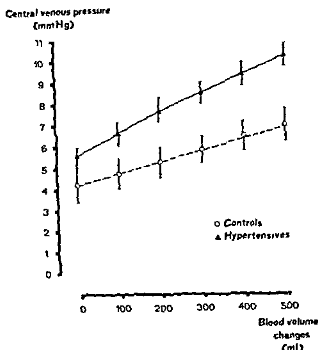


Fig 2 Relationship between blood volume changes and control venous pressure in normal subjects and hypertensive patients. Each point corresponds to the mean value of the group (± 1 standard error of the mean)

Elasticity coefficient (E) of the total vascular bed was calculated as the slope of the relationship Vascular compliance (1/E) was estimated and standardized to body weight The reproducibility of the method was tested in five patients 3 days later The mean variation was 6 3 per cent In three other patients the volume expansion was followed by the withdrawal of the same amount of blood As in the report by Echt and colleagues [8] the slope of the pressure-volume relationship was practically identical during expansion and hemorrhage

Statistical analysis by classical methods (differences of means correlations stepwise regressions) was performed on an HP 9805 A calculator

Results

Hemodynamic parameters (Table II) Blood pressure and total peripheral resistance were elevated ($p < 0.001$) in hypertensive patients Heart rate cardiac index stroke index and right atrial pressure were within normal ranges Cardiopulmonary blood volume was normal

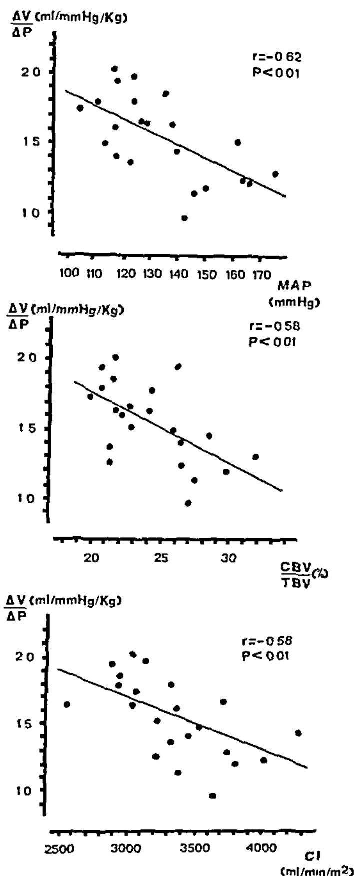


Fig 3 Relationships between the effective compliance (*ΔV/ΔP*) and respectively *mean arterial pressure* (*MAP*) the ratio between cardiopulmonary (*CBV*) and total blood volume (*TBV*) and cardiac index (*CI*) in hypertensive patients.

while total blood volume was reduced significantly

Effective vascular compliance (Figs 1 and 2 Table III) Blood volume expansion induced no change in blood pressure or in heart rate (Fig 1) *Increases* in cardiac index and cardiopulmonary blood volume were similar in magnitude both in normal subjects and hypertensive patients (Fig 1) Fig 2 indicates the changes in central venous pressure *related to the dextran infusion* The intercept of the pressure–volume curves were not significantly different but the slope of the hypertensive group was steeper Effective vascular compliance was significantly reduced in hypertensive patients (1.55 ± 0.60 vs 2.55 ± 0.11 ml/mm Hg/Kg in control subjects ($p < 0.001$) Table III and Fig 3 *demonstrate strong negative* correlations between effective compliance and mean blood pressure ($r = -0.62$ $p < 0.01$) cardiac index ($r = -0.58$, $p < 0.01$) cardiopulmonary blood volume ($r = -0.45$, $p < 0.05$), and the ratio between cardiopulmonary and total blood volume ($r = -0.58$ $p < 0.01$) No comparable *results were observed in control* subjects

Comments

In the control subjects of the present study, the value of the effective compliance was in agreement with previous reports[1-4] *In the permanent* hypertensive patients it was significantly decreased During the dextran infusion a change in blood pressure and/or an altered compliance of *the heart did not seem to influence* the result congestive heart failure was absent basal central venous pressures were within *normal ranges during expansion cardiac output and* cardiopulmonary blood volume increased in the same magnitude as in normal subjects Since the arterial system *is an insignificant fraction* of effective compliance the compliance of the total circulation is mainly related to the properties of the venous side *of the circulation* So the decreased compliance in hypertensive patients strongly suggests the existence of a reduced venous distensibility as previously *observed in experimental* hypertension[1,4,11,12] and in spontaneous hypertension in rats[14,15]

Since the veins are not exposed to the high pressure associated with arterial hypertension decreased venous compliance is unlikely to be

secondary to increased intraluminar pressure However one of the major findings of the study was the strong relationship between compliance and pressure the higher the blood pressure the lower the compliance This correlation suggests that the decreased compliance results from some structural or functional influences common to both arterial and venous bed Genetic differences[1] and/or abnormalities of the ionic and water content of vascular walls[4] have been said to induce structural changes in experimental hypertension and in spontaneous hypertension in rats These defects are not only confined to the arteries Recently they have also been observed in the venous capacitance vessels[17] However the reduced venous distensibility cannot result solely from irreversible structural changes in the presence of effective antihypertensive therapy[2,18] venous distensibility has been shown to return towards normal values This would suggest the influence of neurogenic and/or hormonal factors In favor of this is the decreased effective compliance induced by increased sympathetic activity or elevated levels of norepinephrine[2,4]

Whatever the factors involved changes in venous compliance have important consequences on the over all circulation The decreased distensibility produces a redistribution of blood volume resulting in a shift of blood to the central circulation with a consequent increase in the filling pressure of the heart and an increase in cardiac output[1] In the present study the strong negative relationship between the total body compliance and cardiac output cardiopulmonary blood volume and the ratio between cardiopulmonary and total blood volume are additional evidence In borderline hypertension increased venous return to the heart due to decreased venous compliance may help to account for the increased cardiac output found in these patients[9] In permanent hypertension where blood volume is reduced the decreased compliance may maintain normal cardiac output Thus hypertension should no longer be considered as confined to alterations in the arterial system Changes in the venous bed also exist and require further investigations

Summary

Total effective vascular compliance hemodynamic parameters cardiopulmonary (CPBV) and total blood volumes (TBV) were determined in 31 men including nine normotensive controls and 22 permanent essential hypertensive patients The effective compliance was calculated from the changes in central venous pressure recorded simultaneously with the changes in blood volume obtained after a rapid dextran infusion In hypertensives compliance was significantly reduced (1.55 ± 0.6 vs 2.25 ± 0.11 ml/mm Hg/kg in controls) ($P < 0.001$) and negatively correlated with blood pressure ($P < 0.01$) cardiac index ($P < 0.01$) and the CPBV/TBV ratio ($P < 0.01$) These results suggest that venous compliance contributes to the control of cardiac output in essential hypertension

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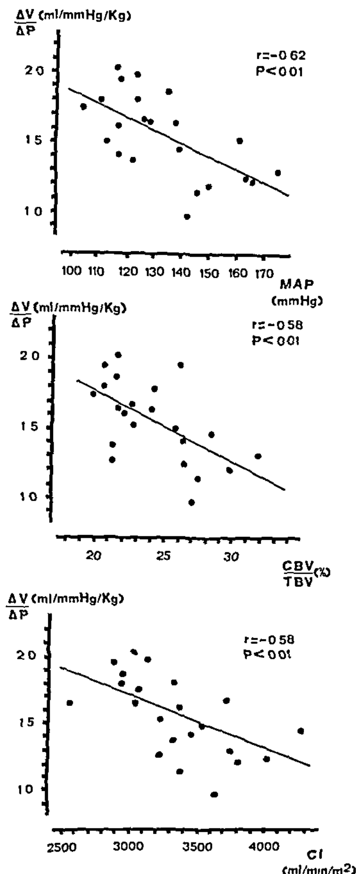


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Whatever the factors involved, changes in venous compliance have important consequences on the over all circulation. The decreased distensibility produces a redistribution of blood volume resulting in a shift of blood to the central circulation with a consequent increase in the filling pressure of the heart and an increase in cardiac output.[2] In the present study, the strong negative relationship between the total body compliance and cardiac output, cardiopulmonary blood volume, and the ratio between cardiopulmonary and total blood volume are additional evidence. In borderline hypertension increased venous return to the heart due to decreased venous compliance may help to account for the increased cardiac output found in these patients.[9] In permanent hypertension where blood volume is reduced, the decreased compliance may maintain normal cardiac output. Thus hypertension should no longer be considered as confined to alterations in the arterial system. Changes in the venous bed also exist and require further *investigations*.

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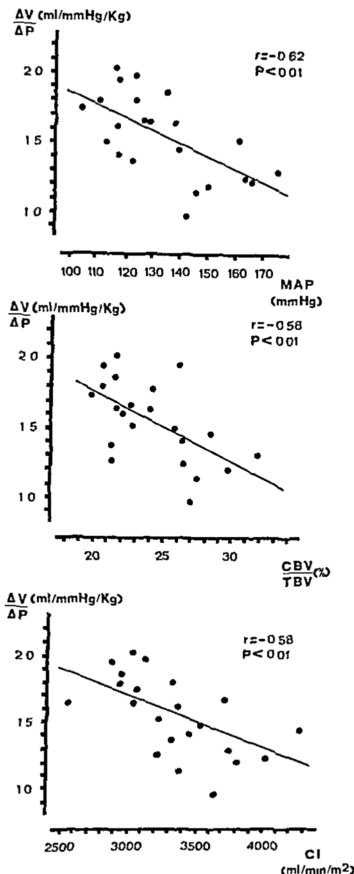


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Effect of pentobarbital anesthesia on ventricular defibrillation threshold in dogs

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Electric shock applied across the chest or directly to the heart is the only practicable means for termination of ventricular fibrillation an otherwise lethal cardiac arrhythmia The shock strength required for defibrillation of the ventricles depends upon body weight in animals and in man[2] but also may be influenced by physiologic factors such as myocardial ischemia electrolyte imbalance drug action and body temperature[4,5] Knowledge of the factors which determine the shock strength necessary for defibrillation is important because a shock which is too weak may fail to defibrillate and a shock which is too strong may damage the heart [6]

All controlled experimental studies of electrical ventricular defibrillation reported to date have used anesthetized animals as subjects—in most cases barbiturate anesthetized dogs In contrast virtually all clinical ventricular defibrillations outside the operating room are carried out in unanesthetized patients in settings such as the coronary care unit or emergency room Recently the barbiturate anesthetized dog has been criticized as a model of normal cardiovascular physiology[7] Since no study can be found in the literature reporting the influence of anesthesia on the efficacy of electrical defibrillation a reasonable question may be raised about the validity of anesthetized animal models used for defibrillation studies

The author has reviewed 58 reports dated 1899 to 1975 concerning the efficacy of electric shock for the termination of cardiac fibrillation in animals In only one study was no anesthesia employed routinely In 37 of 58 studies injectable pentobarbital sodium was the only anesthetic used in a particular species In 10 of the studies thiopental sodium was employed either alone or in combination with inhalation anesthetics and muscle relaxants In six of the studies a mixture of halothane nitrous oxide and oxygen was used often after the induction of anesthesia with intravenous thiopental sodium The use of a variety of other anesthetic agents for defibrillation studies has been reported including sodium barbital glycerol guaiacolate morphine and chloralose In 52 of the 58 studies dogs were used as experimental subjects In particular the pentobarbital anesthetized dog was used in 36 (62 per cent) of the defibrillation studies

Unquestionably anesthetic agents of all kinds have direct effects upon excitable biologic membranes Although the central nervous system is the most important site of action of general anesthetic agents many anesthetics including pentobarbital are known to affect the mechanical and electrical performance of cardiac muscle The amplitude and strength of myocardial contraction are depressed by cyclopropane, diethyl ether nitrous oxide and halothane as well as by barbiturates including pentobarbital secobarbital and thiopental [2] Hydrocarbon anesthetics may depress the rate of activity of the sinus node pacemaker as well as the speed of AV

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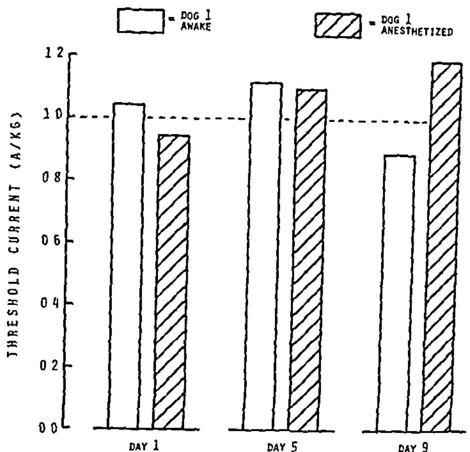


Fig 1 Threshold peak current for ventricular defibrillation in unanesthetized and anesthetized states on successive trials in the same animal On three successive trials the threshold current in the unanesthetized animal was greater than equal to and less than the threshold current after induction of pentobarbital anesthesia Mean threshold before anesthesia = 1 02 A/Kg mean threshold after anesthesia = 1 08 A/Kg Threshold data for the unanesthetized dog were reproducible within ± 10 per cent limits

and intraventricular conduction [13] [17] Significant differences in the response of the dog heart to the AV blocking and arrhythmogenic actions of digitalis glycosides have been reported for animals anesthetized with pentobarbital vs halothane, vs methoxyflurane [18] Cyclopropane halothane and to a lesser extent thiopental are known to sensitize the myocardium to the arrhythmogenic effects of epinephrine [19] Accordingly, it is quite conceivable that anesthetics could alter those parameters of cardiac electrophysiology which determine the success or failure of electrical defibrillation

It is generally accepted that during the induction of anesthesia the relative lipid solubility of general anesthetics and the generous blood flow to the brain cause initial concentration of these drugs in the central nervous system After maintenance of anesthesia for several minutes to several hours, however these drugs become widely redistributed in peripheral tissues including the myocardium [20-22] If there were a significant effect of anesthetics upon the determinants of electrical defibrillation one might reasonably expect a gradual drift of the threshold voltage and current for defibrillation over the course of experiments using anesthetized animals as subjects Control studies demonstrating the presence or absence of such a drift in defibrillation threshold over time intervals greater than one hour have not been reported to date

Accordingly the following studies were undertaken to determine (1) if the induction of anesthesia with intravenous pentobarbital sodium in the dog alters transchest defibrillation threshold and (2) if the maintenance of a stable surgical level of anesthesia with pentobarbital sodium for 8 to 10 hours is associated with a change in the defibrillation threshold

Methods

Study 1 Effect of pentobarbital anesthesia Five dogs of mixed breed weighing 6 to 14 kilograms served as subjects Initially each dog was anesthetized with injectable pentobarbital sodium (Nembutal 50 mg/ml in a 10 per cent

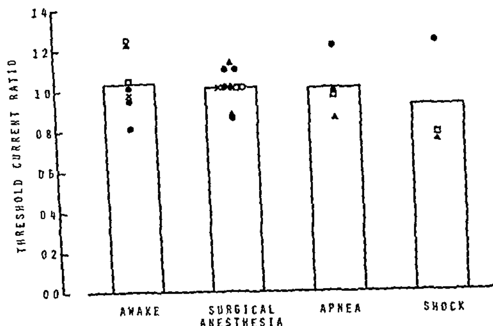


Fig 2 Relative values of threshold peak current for ventricular defibrillation at four levels of anesthesia Awake = no anesthesia surgical anesthesia = spontaneous respiration but no response to surgical stimulation (25 to 30 mg/Kg pentobarbital) apnea = no spontaneous respiration (42 to 51 mg./Kg pentobarbital, cumulative dose) shock = aortic blood pressure less than 50 mm Hg systolic (61 to 77 mg/Kg pentobarbital cumulative dose) Mean threshold current under surgical anesthesia = 1 0 for each animal. Dog 1 *solid circles* Dog 2, *solid triangles* Dog 3 *open circles* Dog 4 *open squares* Dog 5 *crosses*

alcohol 40 per cent propylene glycol vehicle 25 to 30 mg/Kg intravenously) No preanesthetic medication was given A bipolar catheter electrode was placed in the right ventricle of the heart via a right jugular venous cut down using sterile technique Position of the catheter electrode within the heart was verified by recording the catheter tip electrogram and comparing its timing with the electrocardiogram (ECG) Lead II The catheter was stabilized in the jugular vein and the wound was closed with 2 0 silk sutures The external portion of the catheter was protected with an adhesive elastic bandage placed around the neck and a soft collar 8 cm in width After a recovery period of 36 to 72 hours the defibrillation threshold was determined before and after induction of anesthesia with pentobarbital These investigations in unanesthetized and anesthetized subjects were carried out in accordance with National Institutes of Health and institutional guidelines for the use of laboratory animals

Defibrillation threshold in awake unrestrained animals was measured as follows ECG Lead II electrodes were applied to the limbs and the position of the catheter electrode was confirmed by recording the catheter tip electrogram Defibrillating electrodes held in position with rubber straps were applied to the shaved skin of the thorax with electrolytic jelly one centered over the apex beat area and the other in the opposite position on the right chest wall The defibrillating electrodes were stainless steel discs 2 mm thick and 8 to 10 cm in diameter (20 per cent of the animal s chest circumference ± 1 cm) The standard location of each electrode was outlined in ink on the thorax

Ventricular fibrillation was produced by the application of a 1 second train of 60 Hz 2 msec duration rectangular electrical pulses of 5 to 15 volts intensity via the right ventricular catheter Ventricular fibrillation was confirmed by the presence of random waves in the electrocardiogram and by the descending level of consciousness of the subject As the animal lost consciousness it was placed in dorsal recumbency

The defibrillator employed contained a 16 microfarad capacitance a 44 millihenry inductance and a 7 ohm internal resistance in series with the subject A 1 00 ohm 100 watt resistor in series with one electrode was used for measuring

current output The peak output voltage of the defibrillator could be varied continuously from 0 to 7,000 volts The duration of the delivered current pulse, slightly dependent upon subject resistance, was typically 4 to 5 msec The wave form of the current pulse was a heavily damped sinusoid

As soon as possible after the confirmation of ventricular fibrillation, (15 to 45 seconds after endocardial stimulation) a defibrillator shock, calculated to be adequate for defibrillation on the basis of the dog s body weight as described by Geddes and colleagues,[2] was delivered at the time of end expiration The voltage and current applied to the subject were measured using a Tektronics model D 11 dual channel storage oscilloscope Defibrillation was confirmed by return of the femoral pulse and QRS complexes in the electrocardiogram With return of conscious ness the animal was allowed to right itself After a recovery period of about 2 minutes the animal was refibrillated and defibrillation was attempted with a voltage setting 5 to 10 per cent less than that of the previous trial This procedure was repeated until the animal was not defibrillated by the first shock, whereupon a stronger shock was applied immediately to restore cardiac pumping action Threshold voltage and current were defined as the lowest values able to defibrillate the ventricles Only data from the first shock delivered after the onset of fibrillation were used in calculation of threshold In this study thresh old values were considered adequately precise if they differed no more than 10 per cent from values unable to defibrillate the ventricles Deliv ered energy and charge were calculated as described by Babbs and Whistler [5]

Twenty minutes after the defibrillation thresh old was determined in the unanesthetized animal intravenous pentobarbital sodium (25 to 30 mg / Kg) was given to produce surgical anesthesia and the defibrillation threshold measurement was repeated with the animal in dorsal recumbency After a three day recovery period another set of threshold determinations was made in the awake and anesthetized states

On the final day of testing the defibrillation threshold was determined following larger doses of pentobarbital After the routine threshold determination under surgical anesthesia suffi cient intravenous pentobarbital was given to produce apnea and the threshold measurement was repeated Then sufficient intravenous pento barbital was given to produce circulatory shock (defined as systolic blood pressure less than 50 mm Hg measured via a catheter placed in the abdominal aorta) and a final threshold determi nation made within 10 minutes During apnea and shock the animal was maintained using mechanical ventilation sufficient to produce a respiratory minute volume measured with a Wright respirometer, roughly equal to that measured under surgical anesthesia

Study 2 Stability of defibrillation threshold under pentobarbital anesthesia Five dogs of mixed breed 5 to 16 kilograms in weight condi tioned in captivity for a period of at least two weeks and disease free by physical examination were used in this study Each animal was anesthe tized with intravenous pentobarbital sodium (25 to 30 mg /Kg) No other drug except normal saline was administered at any time The trachea was intubated and the animal placed in dorsal recumbency for the duration of the study The urinary bladder was catheterized with a No 8 French filiform catheter connected to a closed volumetric drainage bottle Mean aortic blood pressure was measured using a mercury manom eter, and respiratory minute volume was mea sured with a Wright respirometer Arterial blood pH, pCO and pO were monitored using an Instrumentation Laboratories Model 213 blood gas analyzer Disc electrodes of 8, 10 or 12 cm in diameter (20 per cent of the chest circumference ± 1 cm) were applied to the shaved skin of the right and left hemithoraces with electrolytic jelly and sutured in place One electrode was centered over the apex beat of the heart and the other was located at a corresponding position on the right chest wall, 3 cm cephalad of the left electrode Defibrillation threshold was determined once every hour using the method described for Study 1 The values of mean aortic blood pressure respiratory minute volume urine output arterial blood gases and esophageal temperature were recorded at half hour intervals A stable level of surgical anesthesia was maintained in each animal by the intravenous administration of 2 to 5 mg /Kg maintenance doses of pentobarbital sodium each hour Saline solution 0 9 per cent was given in quantities of 1 to 2 ml /Kg /hr by vein Esophageal temperature was maintained in

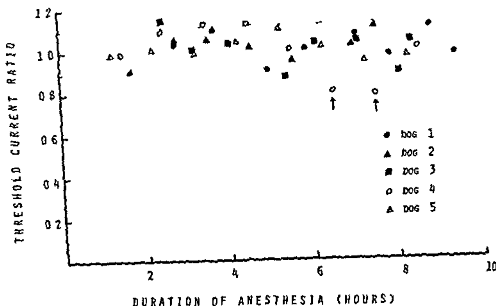


Fig 3 Stability of ventricular defibrillation threshold during pentobarbital anesthesia in dogs *Mean threshold current = 1 0 for each animal Arrows* indicate threshold values obtained during acute respiratory failure

the range of 36 to 39 C with the aid of warm overhead lights

Results

Study 1 In all five dogs comparisons could be made between defibrillation thresholds in the awake and the anesthetized states In one dog three successive comparisons of awake vs anesthetized threshold values were made during a 12 day period Threshold current data for this animal are plotted in Fig 1 The ratios of the threshold peak current for all dogs at all levels of anesthesia to the average threshold under surgical anesthesia for each animal are plotted in Fig 2 No consistent effect of pentobarbital anesthesia on the ventricular fibrillation threshold is evident

Mean values of threshold shock strength in terms of peak current delivered energy and delivered charge per kilogram of body weight are given in Table I One way analyses of variance indicate that the observed effects of anesthesia level upon threshold current energy and charge are far from statistically significant as indicated by the p values in the table

The response of unanesthetized dogs to the fibrillation-defibrillation procedure is worthy of mention Typically the dogs *were not* alarmed by the intracardiac electrical stimulation used to induce fibrillation The loss of cerebral blood flow due to ventricular fibrillation produced initial excitation lasting 5 to 15 seconds which rapidly diminished as the animal lost consciousness Delivery of defibrillating current caused a brief forceful contraction of thoracic and abdominal musculature resulting in vocalization Animals for whom the total circulatory arrest time was less than 30 seconds rapidly regained consciousness and assumed a sitting or standing position Animals for whom the total circulatory arrest time was 30 to 60 seconds did not regain consciousness as soon after defibrillation These animals remained in dorsal recumbency after resuscitation and appeared dazed or tranquilized

Study 2 Stability of defibrillation threshold during anesthesia Fig 3 shows the relative threshold current values for five pentobarbital anesthetized dogs as a function of the duration of anesthesia Relative threshold values were obtained by dividing each threshold current by the mean threshold value for a particular animal No upward or downward drift of the threshold current is evident The variation of individual threshold values seldom exceeds ± 10 per cent limits indicated by dotted lines Interestingly the two extreme points in Fig 2 (Dog 4 *arrows*) were associated with a bout of acute respiratory

current output The peak output voltage of the defibrillator could be varied continuously from 0 to 7 000 volts The duration of the delivered current pulse slightly dependent upon subject resistance was typically 4 to 5 msec The wave form of the current pulse was a heavily damped sinusoid

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Table I Mean defibrillation threshold* at 4 levels of anesthesia

	Awake	Surgical anesthesia	Apnea	Shock	F ratio	p value
Peak current (amps/Kg)	1 25 ± 28	1 22 ± 17	1 21 ± 18	1 13 ± 21	0 21	0 89
Delivered energy (w s/Kg)	1 55 ± 77	1 35 ± 46	1 28 ± 42	1 11 ± 17	0 51	0 68
Delivered charge (m coulombs/Kg)	2 31 ± 41	2 18 ± 25	2 26 ± 43	2 06 ± 39	0 43	0 ,3
Number of observations	7	11	4	3		

± 1 S D

failure (arterial blood gases pH 7 10, pCO_2 54 mm Hg, pO 39 mm Hg) after the institution of mechanical ventilation in this animal the threshold returned to control levels With the exception of this incident all dogs exhibited a stable compensated metabolic acidosis Arterial blood pH, pCO_2, and pO averaged 7 36 ± 0 06,* 33 ± 3 7* and 71 ± 9* respectively Mean arterial blood pressure respiratory minute volume, and urine output were stable during the 8 to 10 hours of pentobarbital anesthesia in all five animals averaging 127 ± 20* mm Hg, 457 ± 168* ml /Kg /minute and 1 2 ± 0 5* ml / Kg /hr, respectively

Discussion

The data of Studies 1 and 2 indicate that the ventricular defibrillation threshold is negligibly affected by either the induction or the maintenance of anesthesia with pentobarbital sodium This finding is important because so many experimental studies of electrical defibrillation have been carried out in anesthetized animals whereas in most clinical situations electrical defibrillation is attempted in unanesthetized humans In view of these results the extrapolation of much hard won animal data to the human situation may be made with significantly greater assurance

In the absence of surgical or pharmacological intervention defibrillation threshold is a stable and reproducible parameter in the pentobarbital anesthetized dog Demonstration of such a stable baseline paves the way for further studies of drug effects in ventricular defibrillation in the presence or absence of myocardial ischemia and for experimental evaluation of alternative techniques of cardiopulmonary resuscitation

Summary

The effect of pentobarbital anesthesia upon the minimal voltage and current required for electrical ventricular defibrillation (the defibrillation threshold) was investigated in dogs Threshold current energy, and charge in five dogs averaged 2 per cent 13 per cent, and 6 per cent less under surgical levels of pentobarbital anesthesia than thresholds in the same animals in the awake, unanesthetized state In dogs given sufficient pentobarbital to produce apnea and supported by mechanical ventilation, threshold current, energy, and charge averaged 3 per cent 17 per cent, and 2 per cent less than comparable awake values These differences were far from statistically significant In a second study five dogs were kept for 8 to 10 hours at a surgical level of anesthesia with pentobarbital sodium Defibrillation threshold current determined at hourly intervals, did not drift outside ± 10 per cent limits Arterial blood gas measurements revealed a stable compensated metabolic acidosis in all animals (pH 7 36 ± 0 06 pCO_2 33 ± 4 mm Hg pO 71 ± 9 mm Hg) These data support the validity of defibrillation studies using animals anesthetized with pentobarbital and indicate the stability of the defibrillation threshold under controlled experimental conditions

* One standard deviation

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Comparison of coronary arteriograms with direct measurements of stenosed coronary arteries in dogs*

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Selective coronary arteriography is extensively used for evaluation of coronary artery disease Postmortem studies however, have suggested that arteriography underestimates the severity of lesions [1-3] A recent preliminary study utilizing an in vivo canine preparation has, on the other hand, suggested that potentially serious overestimations of 15 per cent may occur [4] In order to assess the accuracy of arteriographic estimates of single, discrete lesions we have utilized a similar in vivo preparation in which partial obstruction of coronary arteries was produced by radiolucent plastic cylinders The actual amount of stensosis was determined by microscopic examination of silicone rubber casts of the stenotic regions The physiologic significance of different levels of partial obstruction was determined by measuring the effects of stenoses on phasic coronary blood flow the reactive hyperemic response and the pressure gradient across the mechanical obstruction

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Methods

Sixteen mongrel dogs of either sex weighing between 22 7 kilograms and 34 0 kilograms (average weight, 26 5 kilograms) were premedicated with morphine (3 mg /Kg) 30 minutes prior to induction of anesthesia with sodium pentobarbital (30 mg /Kg) The animals were intubated and connected to a closed circuit anesthetic machine (Ohio Medical Products) for maintenance with a nitrous oxide-oxygen (75 per cent 25 per cent) mixture of gases

A left thoracotomy was performed through the fifth intercostal space The pericardium was incised and the heart suspended in a pericardial cradle The proximal circumflex coronary artery was dissected free to the first major diagonal branch with ligation of small branches as necessary An appropriately sized electromagnetic flowprobe (Statham Model SP2202) was placed on the coronary artery to measure coronary blood flow In 12 of the 16 dogs electromagnetic flow probes (In Vivo Metric Systems) were placed on the proximal aorta to measure aortic blood flow (Fig 1)

Aortic blood pressure was measured utilizing a catheter inserted through the femoral artery and connected to a Statham P23Db pressure transducer Coronary blood pressure was measured with a Khouri Gregg type silicone rubber catheter placed in the circumflex artery distal to the mechanical obstruction and connected to a pres

sure transducer[5] Partial obstruction was produced with radiolucent cylinders 3 mm in length machined from physiologically inert plastic (Lexan) with varying internal diameters as shown in the upper right corner of Fig 1 The cylinders are placed on the coronary artery one at a time to produce controlled amounts of stenosis by completely encircling the artery [1]

A 2 0 silk ligature was passed loosely around the vessel and through plastic tubing and was used to produce temporary complete occlusions for production of reactive hyperemic responses Epicardial and subendocardial ECG leads were placed in the myocardium supplied by the circumflex artery (Fig 1) All parameters were recorded on a Brush Gould (Model 481) eight channel recorder

The dog was then transferred to a room equipped for cineangiography and physiologic parameters were allowed to stabilize Experimental procedures were not initiated until heart rate blood pressure coronary blood flow and aortic flow were steady and unvarying During the coronary arteriography the animal was ventilated with a Bird Mark VII positive pressure respirator A Sones coronary arteriographic catheter was passed from the carotid artery into the aorta and then into the circumflex artery under fluoroscopic guidance Flow and pressure measurements were made before and after the arteriographic catheter was manipulated into the coronary artery Arteriographic contrast material diatrizoate meglumine and diatrizoate sodium (Renografin 76) was injected manually to visualize the circumflex artery lumen while cineangiograms were taken on 35 mm shellburst film at 60 frames/second The films were later read to estimate the amount of partial obstruction produced by the plastic cylinders The arteriograms were magnified (2 times) for inspection and diameters were measured with a millimeter rule The limit of measuring resolution was set as 0 5 mm and fractions were rounded off to this figure The arteriographic estimation of cross sectional area was derived by calculation from the diameter measurement assuming a round lumen Changes in diameter and cross sectional area were expressed as percentage reduction from adjacent unobstructed portions of the vessel

Pressure and flow measurements were made prior to production of partial obstruction with a plastic cylinder A cineangiogram was also

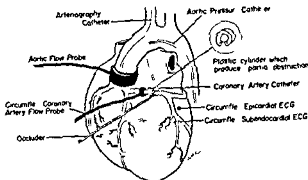


Fig 1 Technique for producing fixed partial obstruction in the left circumflex coronary artery An electromagnetic flow probe of suitable inside diameter is placed on the vessel A plastic cylinder 3 0 mm in length, *as shown in the upper right corner* is selected which will narrow the coronary artery the desired amount and is placed on the vessel To produce temporary complete occlusions a 2 0 ligature is passed around the vessel and through plastic tubing The coronary artery catheter is placed through the vessel wall with the tip in the lumen to measure distal coronary artery blood pressure A cardiac catheter is passed up the femoral artery for aortic blood pressure measurement Epicardial and subendocardial leads for recording electrograms are placed in the myocardium supplied by the circumflex artery A Sones coronary catheter is passed down the carotid artery into the aorta and then into the circumflex artery for selective catheterization of the circumflex coronary artery

obtained during control conditions At least two temporary (20 second) complete occlusions were performed to observe the normal reactive hyperemic responses in the control state and for all stenoses in order to assess reproducibility of the measurement A minimum of three minutes was allowed between temporary complete occlusions for the vasculature to recover

When a cylinder was placed on the coronary artery to produce mechanical stenosis hemodynamic parameters were allowed to stabilize Approximately 10 minutes after the plastic cylinder was placed on the vessel reactive hyperemic responses were observed and another cineangiogram was obtained The first cylinder was removed and control measurements of pressures flows and reactive hyperemias were repeated A different level of stenosis was then produced with a second cylinder and the same protocol was followed If there was sufficient length of the circumflex artery available to permit placing three cylinders on the vessel for casting at necropsy, another level of obstruction was produced with a third cylinder Visual examination and microscopic measurements indicated

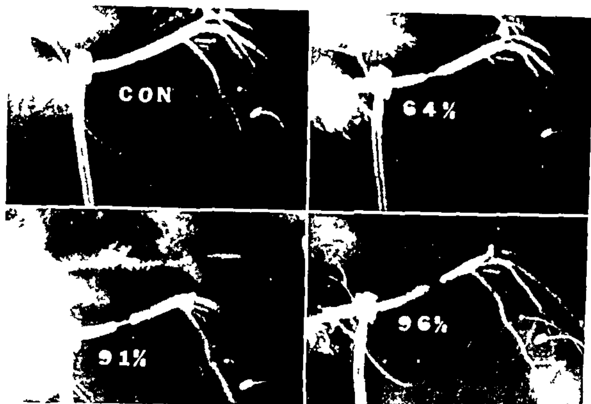


Fig 2 Representative single frame composite of four cineangiographic views from one of the dogs Coronary cineangiograms were obtained under control unobstructed (*CON*) conditions and at three levels of obstruction produced in each dog Because the plastic cylinders are radiolucent the stenotic lumen can be easily visualized The films were magnified (2×) for measurement of lumen diameter with a millimeter rule Cross sectional area was obtained by calculation based on the measured diameter The numbers represent percentage cross sectional area reductions estimated in this manner

that there was little or no change in external diameter of the vessel up to the first diagonal branch In 10 of the 16 dogs three cylinders were used and in six dogs two cylinders were used

At the termination of the experiment, the plastic cylinders were replaced on the vessel producing two or three different amounts of stenosis in series The circumflex artery was cannulated proximally and injected with silicone rubber under physiologic pressure to make a cast of the vessel with the cylinders in place The vessel was then ligated distally and proximally excised, placed in formalin and later sectioned for direct microscopic measurement of reduced diameter and cross sectional area produced by the cylinders

At least three sections were made of control (non obstructed) segments and each stenotic segment The sections were examined under low power microscopy (magnification 25×) and measured with a calibrated grid eyepiece (American Optical Co Scientific Instruments Div) The stenosed diameter and cross sectional area measurements were averaged and then compared with control dimensions Reductions in luminal diameter and area were expressed as percentages and compared with arteriographic estimates using the microscopic measurements as the standard Statistical comparisons were made with the paired t test using $p < 0.05$ as the level of significance The data in the text and figures is presented as mean ± standard deviation

Results

Effects of partial obstruction on hemodynamics Attention was focused on three levels of partial obstruction (1) The amount of stenosis which minimally reduced the reactive hyperemic response without creating a pressure gradient (2) that which produced a measurable pressure gradient across the mechanical obstruction and (3) the amount of stenosis which nearly abolished reactive hyperemia A representative record showing the effects of partial obstruction on hemodynamics in one of the dogs is shown in Fig 4

Data for all of the dogs are summarized in Table I Unobstructed coronary flow increased to a peak of 441 ± 112 per cent of preocclusion flow after a 20 second complete occlusion At the first

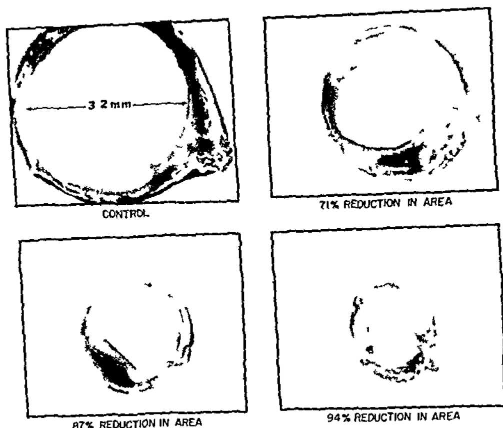


Fig 3 Representative photomicroscopic composite of coronary artery sections from the same dog used in *Fig 2* At least three sections of the injected and fixed coronary arteries were obtained from control and stenotic segments Measurements were averaged and calculated per cent reductions in diameter and cross-section are compared with arteriographic estimates The numbers represent percentage cross-sectional area reduction based on microscopic measurements The lumens of more severely stenosed segments were commonly observed to be irregular *as shown in the lower right and left photomicrographs*

level of obstruction there was no measurable difference between mean aortic and mean circumflex blood pressure but the peak reactive hyperemia after a 20 second occlusion was reduced to 388 ± 83 per cent ($p < 0.001$) of preocclusion flow More severe stenosis producing a small pressure gradient across the stenosis of 9 ± 3 mm Hg (circumflex pressure 9 ± 3 per cent less than simultaneously measured *mean arterial* blood pressure in the aorta $p < .001$) limited the peak reactive hyperemic response to 226 ± 45 per cent of preocclusion flow ($p < .001$) The third level of obstruction nearly abolished reactive hyperemia (126 ± 17 per cent of preocclusion flow) and produced a pressure gradient of 32 ± 11 mm Hg (circumflex pressure 35 ± 12 per cent less than mean arterial blood pressure measured in the aorta $p < .001$)

The characteristic alteration in phasic pattern with increasing partial obstruction is shown in Fig 5 We have previously used the diastolic to systolic (D/S) flow ratio as an index of change in coronary blood flow patterns with increasing partial obstruction[8] The systolic component of flow increases and the diastolic component decreases as the obstruction increases[7] This is reflected in D/S ratios that approach unity with severe levels of partial obstruction which abolish the hyperemic response to temporary complete occlusion A decrease in D/S ratios was not always observed at the first level of obstruction which reduced reactive hyperemia by 25 ± 9 per cent At the two more severe levels of obstruction however a decrease in the D/S ratio was consistently observed (See Table I)

Fig 6 shows the hyperemic effect produced by injecting contrast medium into the circumflex coronary artery during the cineangiogram There is an initial decrease in coronary blood flow which may be due to the high viscosity of the contrast

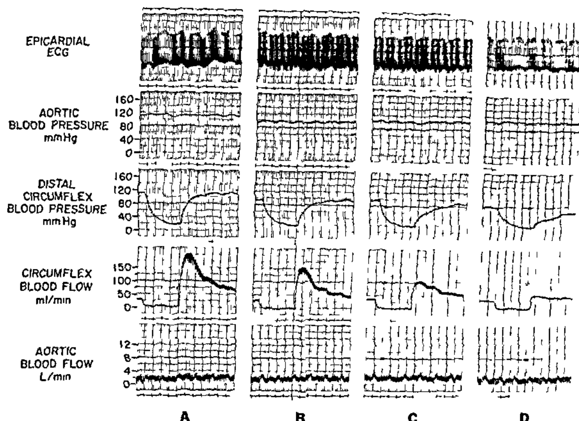


Fig 4 Representative epicardial electrogram aortic and distal circumflex blood pressure circumflex and aortic blood flow from one of the dogs recorded as mean values at slow paper speed *Panel A* shows the normal reactive hyperemic response to a 20 second complete occlusion before placing a plastic cylinder on the circumflex Aortic and distal circumflex blood pressure are identical indicating there is no measurable pressure gradient in the coronary artery due to obstruction by the presence of a flowprobe or the coronary catheter *In panel B* is shown the reactive hyperemic response (21 per cent reduced from control) at the first level of obstruction *In panel C* the reactive hyperemic response is reduced (64 per cent from control) and there is now a pressure gradient of 7 mm Hg across the mechanical obstruction The reactive hyperemic response is nearly abolished (90 per cent reduced from control) and a pressure gradient of 26 mm Hg exists at the third level of obstruction shown *in panel D*

Table I Hemodynamic effects of partial obstruction

	Heart rate (beats/min)	*MABP (mm Hg)*	*MCBP (mm Hg)*	*ΔP (mm Hg)*	*CBF (ml/min)*	*RH maximum (ml/min)*	*% RH reduction*	*D/S ratio*
Control	126 ± 33	98 ± 12	98 ± 12	0	45 ± 24	186 ± 78		2 51 ± 0 37
1st Level of obstruction	119 ± 34	100 ± 11	100 ± 11	0	44 ± 24	161 ± 62	25 ± 9 *	2 44 ± 0 36
2nd Level of obstruction	129 ± 32	95 ± 10	86 ± 12	9 ± 3†	43 ± 25	95 ± 58	64 ± 13	1 82 ± 0 30
3rd Level of obstruction	130 ± 39	94 ± 10	62 ± 17	32 ± 11†	39 ± 18	49 ± 27	93 ± 5†	1 27 ± 0 22†

Abbreviations *MABP* = *mean arterial blood pressure MCBP* = *mean coronary blood pressure (measured distal to mechanical obstruction)* ΔP = pressure gradient across mechanical obstructor (MABP MCBP) CBF = coronary blood flow RH = reactive hyperemia *D/S* ratio = average diastolic *CBF/average systolic CBF (measured over ten cardiac cycles)*
= p < 0 05 = p < 0 01 † = p < 0 001

medium [9] This is followed by an increase in blood flow which is attenuated by partial obstruction Contrast medium induced hyperemia was less than the reactive hyperemia produced by a 20 second complete occlusion in the unobstructed control state and at the first level of obstruction At the second and third levels of obstruction the contrast medium induced hyperemia and reactive hyperemia were very similar

Of the 16 dogs only two showed significant

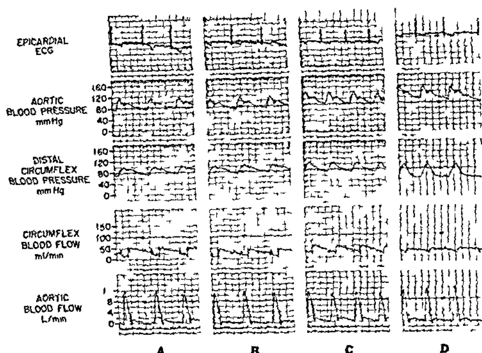


Fig 5 Epicardial electrogram aortic and distal circumflex blood pressure circumflex and aortic blood flow from one of the dogs The phasic flow pattern of normal unobstructed coronary blood flow is shown in panel A with high flow during diastole and low flow during systole (D/S ratio = 3 44) In panel B with obstruction that reduced reactive hyperemia 33 per cent in this dog the pattern is unaltered (D/S ratio = 3 22) At the second level of obstruction (panel C) the phasic flow pattern is altered with an increase in the systolic component of flow and decrease in the diastolic component (D/S ratio = 1.89) With stenosis that reduced reactive hyperemia 95 per cent the flow pattern is markedly changed (D/S ratio = 1 04) and a change in the pattern of distal circumflex blood pressure is also observed (panel D)

changes in the reactive hyperemic response after the coronary catheter was manipulated into the circumflex artery The average change in peak reactive hyperemia in the 14 other dogs after selective catheterization was −2 3 per cent (NS)

Comparison of coronary arteriograms and microscopic measurements A 25 ± 9 per cent reduction in peak reactive hyperemia was produced by stenoses estimated as approximately 50 per cent reductions in diameter and 75 per cent reductions in cross sectional area (Table II) The average differences between diameter and area measurements by the two different methods were statistically nonsignificant

A 64 ± 13 per cent reduction in peak reactive hyperemia and 9 ± 3 mm Hg gradient were created at the second level of obstruction Arteriographic measurements overestimated luminal diameter and area a small but significant amount

The third level of obstruction nearly abolished the reactive hyperemic response (93 ± 5 per cent reduction) and produced a pressure gradient of 32 ± 11 mm Hg across the mechanical obstruction The differences between microscopic and arteriographic measurements of luminal diameter and area again indicated small but highly significant overestimation of lesion severity (See Table II)

Discussion

Previous investigators assessing the accuracy of arteriographic estimation of stenotic dimensions have examined coronary arteries at autopsy and compared them with antemortem arteriograms[1] Such data have always been variably suspect because of the time interval between arteriography and postmortem study and the unknown rate of progression or regression of coronary obstruction In correlative studies comparing human arteriograms made at autopsy and pathological examination of the coronaries the severity of many coronary lesions was underesti

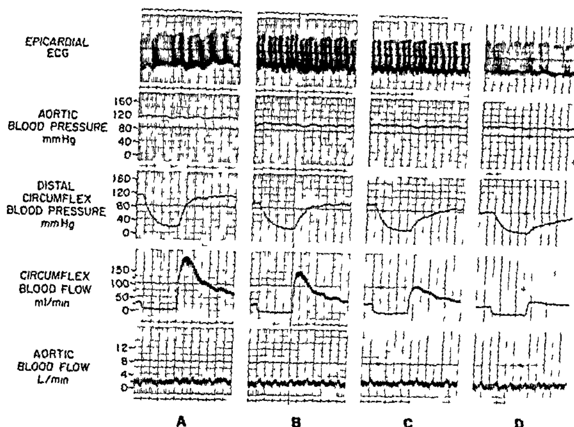


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Table 1 Hemodynamic effects of partial obstruction

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medium[9] This is followed by an increase in blood flow which is attenuated by partial obstruction Contrast medium induced hyperemia was less than the reactive hyperemia produced by a 20 second complete occlusion in the unobstructed control state and at the first level of obstruction At the second and third levels of obstruction the contrast medium induced hyperemia and reactive hyperemia were very similar

Of the 16 dogs only two showed significant

intraluminal concentration of contrast medium In very narrow lesions streaming may occur which could obscure the actual edges of the *internal lumen leading to overestimation* of lesion severity

The least severe stenoses were nearly round in conformation whereas more severe stenoses were irregular The single diameter determined by arteriography depends on the plane viewed since an irregular lesion has several different diameters Consequently the arteriographic estimate of cross sectional area may be inaccurate This may explain part of the disparity observed at more severe levels of obstruction

With more severe stenoses the obstructed region inside the plastic cylinders appeared to progressively change its luminal conformation so that the hemodynamic effects become less severe Approximately 10 minutes were required for hemodynamic conditions to stabilize after the cylinders were placed on the vessel Appropriate time therefore was allowed before obtaining reactive hyperemias and cineangiograms Whether these continued to change slowly between the time of arteriography and histologic section is unknown but *it seems unlikely in view of the* good agreement obtained

This study provides an accurate determination of stenosis dimensions plus the hemodynamic effects produced by the partial obstructions Previous studies have utilized snare devices or pneumatic occluders from which dimension changes were derived from *external* vessel measurements [3] With the technique described here internal *dimension changes were measured* directly with microscopy at necropsy Because the mass of the vessel wall is not totally compressed with constriction the stenosed vessel wall became thickened relative to control vessel wall width (*See Fig 3*) In addition the vessel wall was thrown into folds making the internal *lumen irregular in shape* It is likely that the irregularity and length (3 mm) of the lesions may closely approximate lesions *seen in man* There is a major difference however which should be noted Many of the lesions seen in man are eccentric as well as irregular while the lumen of the vessel segment inside the plastic cylinder was *in the center of the* stenotic region The largest source of error in the estimation of severity of human lesions *however arises from* the fact that there may be no normal vessel near the area of stenosis and consequently the true baseline *from* which to estimate stenosis is unknown Thus if a vessel is uniformly narrowed by 50 per cent no area of stenosis will be identified In this study in the dog normal vessel before and after the stenosis could easily be identified for comparison

Table II Comparison of microscopic measurements with arteriographic estimates of coronary stenoses

	% internal area reduction†		
	A§	M	$\bar{d}$
1st level of obstruction‡ (reactive hyperemia reduced)	74 ± 8	73 ± 9	1 5 (NS)
2nd level of obstruction ‡ (small pressure gradient across obstruction)	83 ± 6	86 ± 7	3 6
3rd level of observation‖ (reactive hyperemia abolished)	96 ± 3	92 ± 3	3 6

Abbreviations A = arteriographic M = microscopic $\bar{d}$ = mean difference
p < 0 05
p < 0 001
†Area measurements were statistically compared with unpaired t tests.
‡*There was no significant difference between microscopic and arteriographic measurements at the first level of obstruction At the second and third level of obstruction arteriography overestimated the extent of area reduction significantly*
§Arteriographic estimates of cross sectional area reduction were obtained by calculation from the diameter estimates made when the *films were read*
‖Due to the irregularity of stenoses at the second and third levels of obstruction diameter estimates are not shown By arteriographic estimation they represent the view through one plane only therefore comparison with microscopic measurements (representing an average value of several different diameters) may not be meaningful.

Effects of partial obstruction on coronary blood flow We have previously demonstrated approximately *10 per cent* reduction in peak reactive hyperemia with 36 ± 10 per cent diameter reduction [6] This coincides well with the 25 ± 9 per cent reduction in peak reactive hyperemia observed with 50 per cent ± 10 per cent reduction in diameter The estimates of stenosis required to produce a pressure gradient or to alter the reactive hyperemic response is similar to previous work from our laboratory and others [6, 1] The loss of reactive hyperemia is said to be due to full arteriolar dilatation which attempts to compensate for *the* resistance of the proximal vessel stenosis [7] Thus the maximally dilated arterioles are unable *to respond* and no

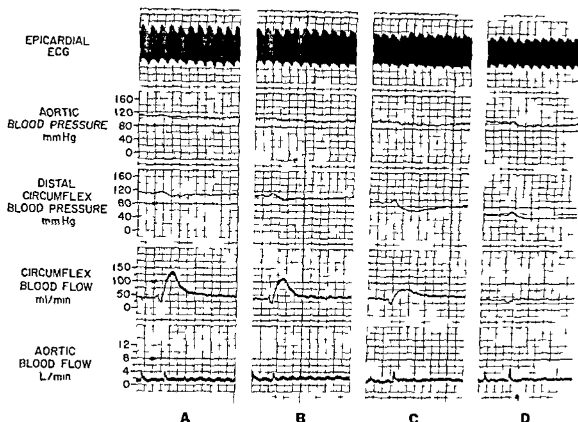


Fig 6 Representative epicardial electrogram aortic and distal circumflex blood pressure circumflex and aortic blood flow from one of the dogs recorded as mean values at slow paper speed *Panel A* shows a normal hyperemic response to the administration of Renografin The average ratio of peak reactive hyperemia to contrast induced hyperemia (RH/CH) for all of the dogs was 0 73 ± 0 13 ($p < 0\ 001$) With partial obstruction that reduced the reactive hyperemia (*panel B*) the contrast induced hyperemia was also less than reactive hyperemia (RH/CH ratio 0 82 ± 14 $p < 0\ 01$) to ischemic stimuli At the second (*panel C*) the third (*panel D*) levels of obstruction however the contrast induced and reactive hyperemias were more similar (RH/CH ratio 0 97 ± 0 15 NS and 1 11 ± 0 15 NS respectively)

mated by arteriography[2, 3] Pepine and associates[4] also demonstrated variance between arteriographic and direct measurements Here, we assessed the accuracy of arteriography under more ideal conditions with single discreet, approximately 3 mm lesions and observed good accuracy with slight overestimation of the degree of occlusion produced by severe lesions (greater than 85 per cent cross sectional area reduction)

Because the left chest wall was open throughout the experiment there was less interference by chest wall lungs and pericardium to obscure the radiographic view although the right portion of all these structures remained as usual The arteriographer had an excellent view of each lesion from which to make estimates of dimension reductions, and although the cineangiograms were performed in only one plane (*See Fig 2*) this was deliberately selected to be optimal

There was no significant difference between arteriographic estimates and direct microscopic measurements with 50 per cent diameter and 75 per cent area reductions in which peak reactive hyperemia was reduced approximately 25 per cent At more severe levels of obstruction, however, the difference was significant since arteriography overestimated the severity of lesions There are several possible reasons to explain this

The heart was constantly moving up and down with the mechanical respiration required because the dog was thoracotomized The viewing plane of the rigid fluoroscopic apparatus was therefore always changing slightly This was compensated to a considerable degree because measurements of the narrowed and normal segments were always made on the same cine frame Nevertheless some rotation could and did occur In addition the stenosis may appear more severe because of the reduced contrast blush effects with large amounts of obstruction Defining the lumen may become more difficult in very narrow regions because as Crawford and colleagues[1] pointed out definition of the lumen depends on the

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post occlusion increase in flow is observed It could be that when the stenosis in the proximal coronary artery reaches a degree of severity which will permit only resting coronary flow, the arteriolar resistance becomes unimportant and no longer controls flow even though the arterioles are not dilated fully

There is a characteristic alteration in the phasic pattern of coronary blood flow with increasing partial obstruction As coronary narrowing becomes more severe, the systolic fraction of flow increases and the diastolic fraction decreases Thus the diastolic-systolic flow ratio approaches 1 0 from the control value of 2 51 ± 0 37 in unobstructed coronary arteries (Table I) With severe stenoses there is a large pressure gradient across the proximal obstruction Also distal coronary pulse pressure increases, perhaps due to the low diastolic resistance offered by dilated arterioles A low diastolic coronary blood pressure could explain the redistribution of flow away from the endocardial muscle layers observed by other investigators, because endocardial flow occurs primarily in diastole [18 0] and pressure may be inadequate to drive sufficient blood flow through the inner layers [1]

Less severe coronary stenoses however, are also potentially dangerous The significance of lesions less than 70 per cent (diameter reduction) is the partial loss of myocardial vasodilator reserve that may jeopardize the heart when blood flow demand is increased and may produce symptoms [2] For example with proximal coronary constriction (if it is assumed that the full proximal coronary lumen is required for maximal flow) during exercise, some point must be reached when coronary vasodilation is inadequate to permit blood flow to meet myocardial demands The blood flow/demand ratio will decrease until ischemia results [3]

Summary

An anesthetized, open chest dog preparation was used to assess the accuracy of arteriography in determining the dimensions of experimentally produced coronary stenoses while monitoring the hemodynamic effects of the lesions Partial obstruction was produced with radiolucent plastic cylinders 3 mm in length made with varying internal diameters Cineangiographic estimates of per cent stenosis were compared with microscopic measurements of silicone rubber casts of the obstructed coronary arteries Three levels of partial obstruction were examined which produced measureable physiologic change

1 Mechanical reduction of coronary luminal diameter of 50 ± 10 per cent and cross sectional area 73 ± 9 per cent (arteriographic estimates 51 ± 7 per cent and 74 ± 8 per cent) produced no pressure gradient but reduced the reactive hyperemic response 25 ± 9 per cent

2 Reduction in diameter of 61 ± 10 per cent and cross sectional area 86 ± 7 per cent (arteriographic estimates 69 ± 9 per cent and 89 ± 6 per cent) produced a pressure gradient of 9 ± 3 mm Hg and reduced reactive hyperemia 64 ± 13 per cent

3 Reduction in diameter of 71 ± 4 per cent and cross sectional area 92 ± 3 per cent (arteriographic estimates 80 ± 6 per cent and 96 ± 3 per cent) produced a pressure gradient of 32 ± 11 mm Hg and reduced the reactive hyperemia 93 ± 5 per cent

There was no significant difference between arteriographic and microscopic measurements at the first level of obstruction which reduced reactive hyperemia 25 per cent The differences at the two higher levels of obstruction however were significant The arteriographic estimates appeared to overestimate the severity of lesions that reduced cross sectional area 85 per cent or more

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The incidence and significance of contraction bands in endomyocardial biopsies from normal human hearts*

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With increasing use of myocardial biopsy as a diagnostic tool, different criteria of pathology have evolved from tissues obtained from biopsy and postmortem specimens We previously reported that contraction bands may be produced artifactually by the biopsy procedure in the fresh, but not the postmortem or perfused fixed normal rat and dog hearts[1] Contraction bands have been used as a morphological index of pathology in conditions such as ischemia cardiomyopathy and catecholamine toxicity Therefore, the aim of this study was to determine the incidence of contraction bands in biopsies from the normal human heart

Method

Endomyocardial biopsy samples were obtained from the right ventricle of 12 normal young human transplant donors by means of the Stanford Caves Schultz bioptome and fixed immediately in 2 ½ per cent glutaraldehyde buffered in 0 1 M sodium cacodylate to pH 7 4 and 10 per cent buffered formalin

Preparation of tissue for paraffin section study by light microscopy The biopsy tissue fixed in formalin was dehydrated, infiltrated, and embedded in paraffin Six micron thick sections were stained with hematoxylin eosin and Masson's trichrome stain

Preparation of tissue for plastic section study by light and electron microscopy The glutaraldehyde fixed tissue was subsequently rinsed in 0 1M sodium cacodylate buffer then post fixed in buffered 1 per cent osmium tetroxide After dehydration in graded concentrations of alcohol and propylene oxide the tissue was embedded in Epon 812 and polymerized overnight at 60° C Samples were sectioned for light and electron microscopy One micron thick sections for light microscopy were stained with toluidine blue or with methylene blue-azure II One thousand A thin sections for electron microscopy were stained in a saturated aqueous uranyl acetate solution for 60 minutes and in lead citrate for four minutes

Method for quantitation of the number of contraction bands All quantitative studies were performed utilizing a 63× planapochromat oil immersion objective lens (N A 1 4) of a Zeiss Universal research microscope To quantitate the light microscopic observations the following previously devised grading system for the number of contraction bands was utilized 0 (absent) 1 (mild) 2 (moderate) and 3 (severe) which represented 0 1 to 5 6 to 10 and 11 or more cells with contraction bands per sq mm of tissue respectively[2]

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Fig 1 Light micrograph of a paraffin section from a normal human right ventricle Note the extensive degree of contraction band formation *(arrows)* (Masson's trichrome stain Bar equals 50 microns)

Results

With hematoxylin–eosin staining of paraffin sections contraction bands appeared eosinophilic whereas with Masson's trichrome staining the bands were easily recognized because of their staining a brilliant red (Fig 1) In plastic sections observed with light microscopy contraction bands were interspersed between the normal cross striations within the myofibril and frequently extended transversely across the entire myofiber (Figs 2 and 3) These contraction bands were present juxtaposed to the intercalated discs and the nuclei as well as between these structures A spectrum of sarcomere lengths existed in which the normal interval between Z lines were reduced to the point at which several intervals merge into one dense homogeneous contraction band With electron microscopy the myofilaments appeared to be arranged haphazardly within the hypercontracted regions which appeared densely osmiophilic (Fig 4)

Contraction bands were observed in biopsy samples from 11 out of 12 hearts and from 10 out of 10 hearts in the Epon and paraffin embedded tissues respectively (Table I) Although the morphology of contraction bands and the definition of cell boundaries were more distinct in plastic than paraffin embedded tissue the latter was adequate for the technique of the quantitation method utilized In the plastic embedded sections nine hearts demonstrated a severe (3rd) degree of contraction band formation whereas one heart showed a moderate (2nd) degree one heart a mild (1st) degree and one heart a zero degree of contraction band formation (Table I)



Fig 2 Light micrograph of a 1 micron thick Epon section from a normal human right ventricle Note the presence of a severe degree of contraction band formation *(arrow)* Intercalated disc *(arrowhead)* (Methylene blue–azure II Bar equals 50 microns)

In the paraffin embedded sections nine hearts demonstrated a severe (3rd) degree and one heart a mild (1st) degree of contraction band formation tissue samples from two hearts were not obtained (Table I)

Discussion

Hypercontraction of sarcomeres below their normal minimal length approximately 1.5 microns results in the appearance of clumped masses of sarcoplasm which have been called contraction bands Contraction bands have been referred to as dense bodies dense bands eosinophilic banding contractures contraction clumps and cytoplasmic banding[3,5] We consider that these contraction bands are caused by excessive interdigitation and folding of the myofilaments Since contraction bands have been present in myocardial tissue associated with various cardiac pathological states their presence has been interpreted as being a part of these pathological processes However in concert with this study of myocardial tissue taken from human hearts is the previous report of myocardial biopsies obtained from completely normal rat and dog hearts which showed a severe degree of contraction band formation[1,2] Therefore the following important question is evoked Is the presence of contraction bands in myocardial tissue a result of a pathological condition or an artifact of technique? This



Fig 3 High magnification light micrograph of the same Epon section of normal heart as seen in *Fig 2* Note the detail within the contraction bands *(arrow)* Intercalated discs *(arrowhead)* (Bar equals 25 microns)



Fig 4 Electron micrograph from a normal human ventricle Note the transition zone *(bottom of figure)* of normal sarcomere lengths merging into an irreversible dense contraction band Also note the disarray of the myofilaments *(arrow)* within the contraction bands (Uranyl acetate and lead citrate Bar equals 1 micron)

Table I The incidence of contraction band formation in biopsy samples obtained from normal human hearts

	Degree of contraction band formation	
Donor	*Epon sections*	*Paraffin sections*
1	3	3
2	1	–
3	3	3
4	3	3
5	3	3
6	0	3
7	3	1
8	3	3
9	3	–
10	2	3
11	3	3
12	3	3

question is partially answered by the previous study in which contraction bands were not seen in the myocardial tissue taken from the same normal animals after a postmorten period of 40 minutes Of further importance even though the endocardial biopsy samples were taken rapidly contraction bands were not seen in hearts perfused with a high concentration of potassium or fixative Consequently we may conclude in general that contraction bands seen in the heart tissue obtained from postmorten tissue or from biopsied tissue obtained after the perfusion of the coronary arteries with high concentrations of potassium or fixative are to be considered due to the pathological condition and not the result of an artifact of preparation On the other hand contraction bands present in tissues obtained from endocardial biopsies may have been produced artifactually however the possibility that a pathological state may also exist in this myocardial tissue cannot be ruled out

What is the genesis of these artifactually produced contraction bands in normal hearts? From the previous study of myocardial tissue obtained under various conditions in lower animals the infusion of fixative into the coronary arteries did not produce contraction bands consequently fixative alone applied to the endocardial biopsy specimen itself is not responsible for contraction band formation Since the inhibition of membrane depolarization with the infusion of high concentration of potassium prevented the formation of contraction bands we may conclude that the mechanical aspect of the biopsy procedure does not directly activate the contractile machinery From these results the following

hypotheses were developed for the mechanism of contraction band formation The formation of contraction bands are due to the depolarization of the myocardial cell by the biopsy procedure resulting in activation of the contractile apparatus together with sarcomeres capable of hypercontraction because their shortening is unopposed

The results of the present study utilizing normal human hearts demonstrates as in the previous animal study that contraction bands cannot be relied upon as an index of pathology in tissues obtained during biopsy However contraction bands may be considered a morphological index of pathology in myocardial tissue obtained 40 minutes postmortem

Summary

With increasing use of myocardial biopsy as a diagnostic tool different criteria of pathology have evolved from tissues obtained from biopsy and postmorten specimens We reported that contraction bands may be produced artifactually by the biopsy procedure in the fresh but not the postmorten or perfused fixed normal rat and dog hearts Contraction bands have been used as a morphological index of pathology From 12 normal human transplant donors endomyocardial biopsy samples were obtained from the right ventricle were fixed immediately and then processed for light and electron microscopy Contraction bands were quantitated by assigning 0 1 2 and 3 to represent 0 1 to 5 6 to 10 and 11 or more cells per square millimeter with contraction bands A large number of contraction bands were present in 11 out of 12 hearts 3rd 2nd 1st and zero degrees of contraction bands were present in 11 0 1 and 0 samples respectively We conclude that contraction bands may be produced artifactually in normally human hearts and based upon the rat and dog study that the determinants of contraction band formation are activation of the contractile machinery by the biopsy procedure together with sarcomeres capable of hypercontraction because their shortening is unopposed

Furthermore contraction bands may be considered a morphological index of pathology in tissue obtained postmortem and after perfusion fixation but not in tissue obtained from biopsies

The authors wish to acknowledge the technical assistance of Marilyn Masek Bob Heusser and A Richard Soto

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Creatine phosphokinase MB isoenzyme in hypothermia Case reports and experimental studies

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The determination of the total activity of serum creatine phosphokinase (CPK) and its use as a specific test for acute myocardial damage is well recognized [1] However, since total serum CPK activity can be elevated by other conditions,[2] the appearance in serum of the MB isoenzyme of CPK (CPK MB) has been proposed as a more specific indicator of acute myocardial infarction [3,4] The occurrence of greater than 2 per cent of the MB isoenzyme of CPK has been reported to be in the serum of patients with muscular dystrophy [5] muscular inflammatory disorders [6] ischemic rhabdomyolysis with myoglobinuria carbon monoxide poisoning malignant hyperthermia [8] Reye s syndrome [9] and in certain cases of minor cardiac trauma [10] However these conditions are clinically distinct from acute myocardial infarction, and there is usually little difficulty in distinguishing among them

Six critically ill patients with profound hypothermia are reported in whom the CPK MB isoenzyme was detected without other clinical or postmortem evidence of myocardial infarction To investigate the possible source and pattern of CPK appearance in serum, we studied the effects of similar levels of hypothermia in mongrel dogs

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Supported by Cardiovascular Research Institute Training Grant HL-05251

Materials and methods

Twenty mongrel dogs weighing from 13 5 to 20 6 kilograms were studied The dogs were anesthetized with intravenous pentobarbital, 25 mg / Kg body weight intubated and ventilated on a Harvard ventilator for 24 hours Periodic additional intravenous doses of pentobarbital were required to maintain anesthesia Central body temperature was monitored with a thermistor placed high in the rectum The electrocardiogram was monitored on a DR 12 Electronics for Medicine optical recorder Dogs which required drugs to control severe sinus bradycardia or cardioversion for ventricular fibrillation were excluded from the study All animals were killed at the end of the period of anesthesia

In seven dogs after induction of anesthesia and control blood sampling serial blood samples were drawn at 1 to 2 hour intervals for 24 hours for determination of total CPK activity In four of the dogs deep hypothermia (23 to 25° C) was induced by total body cooling with externally applied ice bags the duration of hypothermia was limited to 6 hours The subsequent rate of rewarming was controlled by a heating pad In

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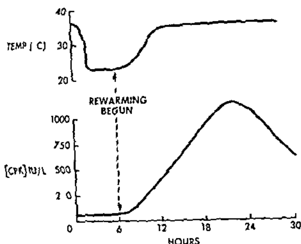


Fig 1 Body temperature and total serum CPK activity in a dog subjected to 6 hours of deep hypothermia

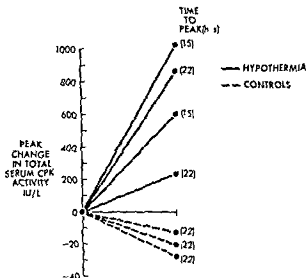


Fig 2 Peak observed changes in serum CPK activity in seven anesthetized dogs followed for 24 hours Four dogs *(solid lines)* were subjected to an initial 6-hour period of hypothermia (23 to 24 C) The remaining three dogs *(broken lines)* were maintained at normal body temperatures

the remaining three dogs anesthesia was continued for 24 hours with the animals maintained at normal body temperature

In 13 dogs a midline sternotomy was performed Control biopsy specimens were obtained from the anterolateral wall of the left ventricle and from striated muscle from two locations in the cervical paraspinous musculature After 22 hours of anesthesia biopsy specimens were again obtained from adjacent myocardial and striated muscle areas In seven of these dogs deep hypothermia was induced as just described and similarly maintained for 6 hours In the remaining six dogs normal body temperature was maintained for the duration of anesthesia

Serum samples from experimental animals and from patients were analyzed for total CPK activity by the Rosalki method Results were expressed in I U /L at 25 C Creatine phosphokinase isoenzyme analysis was performed by electrophoretic separation and fluorescent scanning according to the method of Elevitch [2] Results were expressed in per cent of the total scanned area of MM MB and BB isoenzyme

Biopsied samples 100 mg of wet tissue from left ventricle and striated muscle were homogenized in the cold by mortar and pestle in 1000 µL of 0 1 mole/L using tris hydrochloride buffer containing 0 01 mole/L cysteine at pH 8 0 The resulting homogenate was spun at 3 000 r p m for 20 minutes The supernatant was analyzed for total CPK activity as noted previously [1] The unspun homogenate was analyzed for total protein concentration by the Biuret method A 40 ml sample was diluted with 2 8 ml of Biuret solution and allowed to stand for 30 minutes at 25° C The specimen was read at 540 nm on a Gilford DU spectrophotometer with no filter Readings were compared with a standard albumin curve (bovine fraction V New England Reagent Laboratory) and the results are expressed in mg /L total protein At least three separate samples of homogenate were analyzed Creatine phosphokinase activity per mg of protein was obtained by dividing the total CPK concentration by the total protein concentration All experimental specimens were analyzed within 2 hours after sampling

Results

Fig 1 shows the typical serum pattern of CPK activity observed in one of the hypothermic dogs similar results were observed in the other three dogs Increased CPK activity was noted after rewarming was begun but before normothermia was reached attaining a maximum 15 to 22 hours after hypothermia was initiated In the three normothermic control dogs observed for 24 hours total serum CPK activity actually fell (Fig 2) No serum CPK MB isoenzyme activity was noted in any dog

After hypothermia, both heart and striated

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medical management but over the ensuing 3 weeks repeated bouts of sepsis occurred and the patient died of *Pseudomonas* pneumonia During this period the previously low QRS and T voltage resolved and there was no change to suggest myocardial infarction

At postmortem examination the gallbladder was obstructed by a large stone The heart had a normal configuration without a pericardial effusion Moderate coronary atherosclerosis was present with narrowing up to 50 per cent There were no thrombi and no microscopic or gross evidence of myocardial infarction

Case No 5 A 65-year old unconscious woman was admitted to San Francisco General Hospital Medical Center on December 15 1975 She was lethargic with multiple bruises over the fac arms and trunk. Blood pressure was unobtainable pulse was 50 beats/minute respiration 20 breaths/minute and rectal temperature 23 3 C The patient had neurologic evidence of left carotid occlusion involving the left hemisphere and hypothalamus Other than marked kyphoscoliosis and evidence of dehydration, the remainder of the examination was negative Hemoglobin was 13 8 Gm /100 ml and the white blood cell count was within the normal range Arterial blood pH was 7 47 Pco 27 mm Hg and Po 50 mm Hg. Blood glucose was 177 mg./100 ml blood urea nitrogen 168 mg /100 ml sodium 146 mEq /L. potassium 3 4 mEq /L. chloride 104 mEq /L. and carbon dioxide 13 mEq /L. The chest roentgenogram showed no abnormalities. The electrocardiogram showed sinus bradycardia with an elevated J junction consistent with hypothermia The SGOT level was 230 I U /L. and LDH 365 I U /L with LDH (25 per cent) greater than LDH (16 per cent) Total CPK was 76 I U /L with 12 per cent MB and 4 per cent BB isoenzyme No myoglobin was found in serum or urine Over the ensuing 36 hours the hemodynamic and pulmonary status deteriorated and the patient died

Postmortem examination revealed calcified coronary arteries and luminal narrowings of 50 per cent There was however no gross or microscopic evidence of coronary occlusion or myocardial infarction

Case No 6 A 91 year-old unresponsive woman was admitted to San Francisco General Hospital Medical Center on Februray 9 1976 She was lethargic cachectic and dehydrated and had no evidence of trauma Blood pressure was 140/ 0 mm Hg pulse 96 beats/minute respiration 30 breaths/minute and rectal temperature 33 8 C There was evidence of bilateral pneumonia a right pleural effusion, and abdominal ileus There were no localizing neurologic findings. Hemoglobin was 11 2 Gm /100 ml. and white blood cell count 8,000/μL. with a marked shift to the left Urine was clear with a negative benzidine test Blood urea nitrogen was 71 mg /100 ml sodium 150 mEq /L potassium 5 0 mEq /L chloride 113 mEq /L and carbon dioxide 11 mEq /L. Arterial blood pH was 7 33 Pco 29 mm Hg and Po 53 mm Hg Serum amylase was 11 8 01 U /L SGOT was 140 I U /L and LDH 465 I U /L. Serial enzyme determinations are shown in Table III The electrocardiogram showed normal sinus rhythm and nonspecific ST and T wave changes Intravenous infusion of fluids, antibiotics and steroids was started Renal, hemodynamic intestinal and mental status improved over the next 20 days and the patient was transferred to a chronic care facility Serial electrocardiograms failed to show any evidence of myocardial infarction.

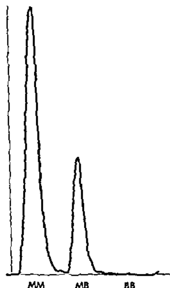


Fig 3 Creatine phosphokinase (CPK) isoenzyme electrophoresis and fluorescence scan from Case No ? The total CPK activity was 1 015 I.U /L. The area under the MB isoenzyme portion of the scan was 27 per cent of the total area.

Discussion

The presence in serum of CPK MB isoenzyme activity has been shown to be a sensitive and specific indicator of ischemic myocardial injury[3]. In addition it has been suggested that serial measurement of CPK MB isoenzyme activity may indicate not only the presence but also the extent of myocardial infarction[11] Therefore it is important to document the clinical circumstances in which CPK MB isoenzyme appears in serum particularly those situations that can be confused clinically with acute myocardial infarction All the patients described in this report presented with serious medical problems problems which may be associated with or result from acute myocardial infarction Two of the six patients presented with cerebrovascular accidents Case No 3 presented with respiratory acidosis Case No 6 had marked serum amylase elevation, initially suggesting bowel infarction or pancreatitis Case No 4 had evidence of profound hypoglycemia and sepsis There was no evidence of myoglobinuria in any patient The only common factor among these patients was the presence of profound hypothermia

Of the three patients who died all showed varying degrees of coronary atherosclerosis but no gross or microscopic evidence of acute occlusion or myocardial infarction Of the survivors

Table I Tissue CPK changes in experimental hypothermia induced in dogs

Tissue	*Mean total CPK activity (I U /mg protein ± 1 S D) After 24 hours of anesthesia*		
	All control dogs (n = 13)	*Under normothermic conditions (n = 6)*	*After an initial 6 hours of hypothermia (23 to 24° C) (n = 7)*
Left ventricle	15 2 ± 4 5	15 8 ± 6 3	11 8 ± 4 4*
Striated muscle	22 0 ± 5 6	22 9 ± 4 8	16 5 ± 4 6†

*P < 0 02 paired Student s t test (value versus control)
†P < 0 01 paired Student s t test (value versus control) and unpaired (value versus mean of anesthesia group)

muscle specimens showed an average reduction of 21 per cent in CPK activity from the initial value (Table I) in both cases No reduction in CPK activity from either heart or striated muscle was observed in the open chest preparations subjected to anesthesia alone (Table I)

Case reports (Table II)

Case No 1 An 85 year old comatose woman was admitted to San Francisco General Hospital Medical Center on December 5 1975 On admission the rectal temperature was 25 6 C pulse 50 beats/minute blood pressure 160/0 mm Hg and respiration 30 breaths/minute Physical findings were consistent with a mid brain or intracerebral cerebrovascular accident Laboratory studies were as follows hematocrit 44 per cent white blood cell count 9400/μL arterial blood pH 7 45 Pco_2 26 mm Hg sodium 127 mEq /L and potassium 3 9 mEq /L Urine was clear with 3+ glucose and a negative benzidine test Chest roentgenograms showed a right upper lobe infiltrate The electrocardiogram showed complete left bundle branch block and atrial fibrillation with a ventricular rate of 50 to 70 beats/minute with no change from a tracing taken 9 months previously Total serum CPK in sample obtained on admission was 131 I U /L with 5 per cent MB and trace BB isoenzymes

Despite supportive medical care the patient died 14 hours after admission Postmortem examination revealed an acute right intracerebral hemorrhage with mid brain herniation The coronary arteries showed moderate atherosclerosis without occlusive disease Gross and microscopic heart examination showed no evidence of recent or old myocardial infarction

Case No 2 An 83-year old comatose woman was admitted to San Francisco General Hospital Medical Center on October 28 1975 On admission the rectal temperautre was 22 2° C heart rate 30 beats/minute blood pressure 90/0 mm Hg and respiration 16 breaths/minute She appeared emaciated and severely dehydrated with diffusely increased muscle tone and had an early sacral decubitus ulcer A lumbar puncture showed low cerebrospinal fluid pressure only The hematocrit was 32 per cent with a white blood cell count of 9?00 μL Arterial blood pH was 7 36 Pco_2 34 mm Hg Po 104 mm Hg while breathing 100 per cent oxygen Blood urea nitrogen was 52 mg /100 ml sodium 142 mEq /L potassium 2 3 mEq /L and glucose 365 mg /100 ml The urine was clear with a 1+ positive benzidine test and 5 to 10 red blood cells per high power field The chest roentgenogram showed no abnormalities The electrocardiogram showed sinus bradycardia QT = 0 6 seconds and left ventricular hypertrophy The patient gradually responded to medical treatment with resolution of coma hypothermia dehydration and normalization of blood potassium and glucose levels The urine remained clear with no evidence of myoglobin Serial electrocardiograms showed resolution of QT prolongation and no evidence of myocardial infarction Serum enzyme data are summarized in Table III The CPK isoenzyme pattern on the second day after admission is shown in Fig 3 The patient was transferred 16 days after admission to a convalescent hospital

Case No 3 A 24 year old comatose man without spontaneous respiration after an overdose of barbiturates was admitted to San Francisco General Hospital Medical Center on December 2 1975 The rectal temperature was 34 4° C blood pressure 142/88 mm Hg pulse 84 beats/minute and respiration 20 breaths/minute after intubation Physical examination revealed no other abnormalities Hemoglobin was 15 6 Gm /100 ml and white blood cell count 11 700/μL While being maintained on 100 per cent oxygen arterial blood pH was 6 90 Pco 88 mm Hg and Po_2 250 mm Hg Hypercarbia resolved promptly after intubation The urine was clear with a negative benzidine test The roentgenogram showed no abnormalities The electrocardiogram showed normal sinus rhythm right bundle branch block QT prolongation and nonspecific ST T wave changes The serum CPK was 227 I U /L with 4 per cent MB isoenzyme On the day after admission there was still 3 per cent MB isoenzyme with a total CPK of 282 I U /L Serum glutamic oxaloacetic transaminase (SGOT) and lactic dehydrogenase (LDH) remained within normal limits The coma gradually resolved and the patient was extubated and finally discharged after 5 days Serial electrocardiograms showed resolution of QT prolongation but no evolutionary changes to suggest an acute myocardial infarction The patient had no history of prior cardiac disease and there was no family history of premature coronary disease

Case No 4 A 68 year old unresponsive man who was a chronic alcoholic was admitted to San Francisco General Hospital Medical Center on November 22 1975 The patient was emaciated and had a rectal temperature of 31 6° C blood pressure of 80/60 mm Hg pulse 100 beats/minute and respiration 20 breaths/minute There was no evidence of trauma Except for moderate hepatomegaly no other physical abnormalities were apparent Hemoglobin was 11 2 Gm /100 ml and white blood cell count was 21 ?00/μL Arterial pH was 7 49 Pco 34 mm Hg and Po 65 mm Hg The urine was clear with 2 red blood cells per high power field and 1+ positive benzidine test Blood glucose was 15 mg /100 ml Serial enzymes are shown in Table III The chest roentgenograms showed no abnormalities The electrocardiogram showed arterial fibrillation at a rate of 100 beats/minute and low QRS and T wave voltage The patient responded initially to

medical management but over the ensuing 3 weeks repeated bouts of sepsis occurred and the patient died of *Pseudomonas* pneumonia. During this period the previously low QRS and T voltage resolved and there was no change to suggest myocardial infarction

At postmortem examination the gallbladder was obstructed by a large stone The heart had a normal configuration without a pericardial effusion Moderate coronary atherosclerosis was present with narrowing up to 50 per cent There were no thrombi and no microscopic or gross evidence of myocardial infarction

Case No 5 A 65-year old unconscious woman was admitted to San Francisco General Hospital Medical Center on December 15 1975 She was lethargic with multiple bruises over the face arms and trunk Blood pressure was unobtainable pulse was 50 beats/minute respiration 20 breaths/minute and rectal temperature 23 3 C The patient had neurologic evidence of left carotid occlusion involving the left hemisphere and hypothalamus Other than marked kyphoscoliosis and evidence of dehydration the remainder of the examination was negative Hemoglobin was 13 8 Gm /100 ml and the white blood cell count was within the normal range Arterial blood pH was 7 47 Pco 27 mm Hg and Po 50 mm Hg. Blood glucose was 177 mg /100 ml blood urea nitrogen 168 mg /100 mL sodium 146 mEq /L potassium 3 4 mEq /L chloride 104 mEq /L and carbon dioxide 13 mEq /L The chest roentgenogram showed no abnormalities The electrocardiogram showed sinus bradycardia with an elevated J junction consistent with hypothermia The SGOT level was 30 I U /L and LDH 365 I U /L with LDH (25 per cent) greater than LDH (16 per cent) Total CPK was 76 I U /L with 12 per cent MB and 4 per cent BB isoenzyme No myoglobin was found in serum or urine Over the ensuing 36 hours the hemodynamic and pulmonary status deteriorated and the patient died

Postmortem examination revealed calcified coronary arteries and luminal narrowings of 50 per cent There was however no gross or microscopic evidence of coronary occlusion or myocardial infarction

Case No 6 A 91 year-old unresponsive woman was admitted to San Francisco General Hospital Medical Center on Februray 9 1976 She was lethargic cachectic and dehydrated and had no evidence of trauma Blood pressure was 140 0 mm. Hg pulse 96 beats/minute respiration 30 breaths/minute and rectal temperature 33 8 C There was evidence of bilateral pneumonia a right pleural effusion and abdominal ileus There were no localizing neurologic findings Hemoglobin was 11 2 Gm /100 ml and white blood cell count 8,000/µL with a marked shift to the left Urine was clear with a negative benzidine test Blood urea nitrogen was 71 mg /100 ml sodium 150 mEq /L potassium 5 0 mEq /L chloride 113 mEq /L and carbon dioxide 11 mEq /L Arterial blood pH was 7.33 Pco 29 mm Hg, and Po 53 mm Hg Serum amylase was 11,8 0 I U /L SGOT was 140 I U /L and LDH 455 I U /L Serial enzyme determinations are shown in Table III The electrocardiogram showed normal sinus rhythm and nonspecific ST and T wave changes. Intravenous infusion of fluids antibiotics and steroids was started Renal hemodynamic intestinal and mental status improved over the next 20 days and the patient was transferred to a chronic care facility Serial electrocardiograms failed to show any evidence of myocardial infarction

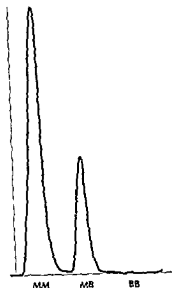


Fig 3 Creatine phosphokinase (CPK) isoenzyme electrophoresis and fluorescence scan from Case No 2 The total CPK activity was 1 015 I U /L The area under the MB isoenzyme portion of the scan was 27 per cent of the total area

Discussion

The presence in serum of CPK MB isoenzyme activity has been shown to be a sensitive and specific indicator of ischemic myocardial injury[3] In addition it has been suggested that serial measurement of CPK MB isoenzyme activity may indicate not only the presence but also the extent of myocardial infarction[1, 15] Therefore it is important to document the clinical circumstances in which CPK MB isoenzyme appears in serum particularly those situations that can be confused clinically with acute myocardial infarction All the patients described in this report presented with serious medical problems problems which may be associated with or result from acute myocardial infarction Two of the six patients presented with cerebrovascular accidents Case No 3 presented with respiratory acidosis Case No 6 had marked serum amylase elevations initially suggesting bowel infarction or pancreatitis Case No 4 had evidence of profound hypoglycemia and sepsis There was no evidence of myoglobinuria in any patient The only common factor among these patients was the presence of profound hypothermia

Of the three patients who died all showed varying degrees of coronary atherosclerosis but no gross or microscopic evidence of acute occlusion or myocardial infarction Of the survivors

Table II Summary of patient data

Patient No	Age (yr)	Sex	Admitting diagnosis	Admitting rectal temp (° C)	Maximum observed values: Total LDH (I U /L)	% LDH_1	% LDH_2	Total CPK (I U /L)	% MB	Outcome
1	85	F	Cerebrovascular accident	25 6	–	–	–	131	5	Died 14 hours after admission
2	83	F	Accidental hypothermia	22 2	495	37	42	1884	32	Discharged
3	24	M	Drug overdose	34 4	–	–	–	227	4	Discharged
4	68	M	Hypoglycemia and sepsis	31 6	385	–	–	428	7	Died 21 days after admission
5	65	F	Cerebrovascular accident	23.3	365	16	25	76	12 (4% BB)	Died 36 hours after admission
6	91	F	Dehydration	33 8	433	23	27	805	4	Discharged

Table III Serum enzyme data obtained during hospital course of patients

Patient and parameter	Day 1	Day 2	Day 3	Day 4	Day 5	Day 7
Patient No 2						
Temperature (° C)	22 2	35 5	36 7	37 0	36 7	36 7
Total CPK (I U /L)	1884	1015	1250	383	164	122
% MB	32	27	Not done	7	3	Not done
LDH (I U /L)	365	381	Not done	495	Not done	475
% LDH_1	36	40	Not done	37	Not done	32
% LDH	41	43	Not done	42	Not done	40
Patient No 4						
Temperature (° C)	31 6	34 6	38 3	–	36 8	–
Total CPK (I U /L)	428	287	124	–	58	–
% MB	7	6	4	–	Trace	–
LDH (I U /L)	285	395	355	–	323	–
Patient No 6						
Temperature (° C)	33 8	36 3	37 2	–	–	–
Total CPK (I U /L)	805	648	399	–	–	–
% MB	4	10	4	–	–	–
LDH (I U /L)	356	433	520	–	–	–
% LDH	20	23	–	–	–	–
% LDH	26	27	–	–	–	–

CPK = creatine phosphokinase LDH = lactic dehydrogenase

there was inadequate clinical evidence to establish the presence of a discrete acute myocardial infarction Case No 3 was young without any personal or family history of premature heart disease and had no electrocardiographic evidence of infarction Despite the advanced age of the two remaining patients (Cases No 2 and 5) and the severity of their underlying medical problems there was no electrocardiographic evidence of infarction no evidence of congestive heart failure to suggest pump dysfunction and no evidence of an abnormal LDH isoenzyme pattern

We undertook a series of experiments in dogs to determine whether or not these clinical observations could be reproduced under controlled conditions In these experiments, dogs made hypothermic for only 6 hours showed a consistent rise in total serum CPK activity This increase in enzyme activity occurred during the period of rewarming before body temperature had returned to normal and rose to a peak 15 to 22 hours after hypothermia was begun In the control experiments after 24 hours of anesthesia under normothermic conditions serum CPK actually decreased This may reflect the effects of decreased muscle activity analogous to that observed in hospitalized patients on bed rest [11]

In the animal experiments the changes

observed in total enzyme activity were solely the result of increased CPK MM isoenzyme activity The CPK MB isoenzyme was not observed in any animal serum sample This is to be expected since CPK MB isoenzyme makes up a much smaller fraction of total myocardial CPK activity in dogs than it does in man [15]

Because we did not observe changes in serum CPK MB isoenzyme activity in these animal studies it might be difficult to comment on the source of this isoenzyme in the patients However data from the open chest animal studies indicate that the increase in total serum CPK activity due to hypothermia results from a 21 per cent reduction in total CPK activity in both striated and myocardial muscle The peak total serum CPK activities observed in the closed chest studies are lower than would be expected for such massive cellular CPK release a finding similar to that observed in myocardial infarction The reason for this discrepancy was not specifically investigated but must be due to either increased local enzyme catabolism or decreased enzyme synthesis due to hypothermia Regardless these findings in the dog studies indicate that the changes in total CPK activity observed in the patients with hypothermia probably reflect enzyme release from both striated and myocardial muscle cells

In addition the source of the serum CPK MB isoenzyme observed in the hypothermic patients was probably myocardial cellular release We believe that this conclusion is justified if we can extrapolate our findings of a reduced total myocardial CPK activity owing to hypothermia from dogs to man Because the MB isoenzyme makes up a larger fraction of total myocardial CPK activity in man than in dogs any reduction in total cardiac cellular enzyme activity in man may be associated with the appearance of this isoenzyme in serum The level of CPK MB observed also supports a cardiac origin for the isoenzyme We noted that the MB isoenzyme constituted 4 to 27 per cent of total CPK activity In man the only tissue that contains greater than 4 per cent MB isoenzymes is the myocardium

How the changes that we observed in myocardial CPK activity relate to actual irreversible myocardial damage is not entirely clear Kjekshus and Sobel showed that depression of myocardial CPK activity is a useful indicator of the extent of irreversible tissue damage However histochemical studies performed in rats with ischemic injury induced by isoproterenol demonstrated a marked early reduction of cellular CPK activity followed by a gradual return of enzyme activity to almost normal levels after 4 hours [7] In that study only the subendocardium underwent necrosis without recovery of CPK activity However methods were not used to determine if the cytoplasmic protein with CPK activity was actually lost from reversibly damaged cells or if enzyme activity was inhibited locally with no contribution to serum enzyme activity changes Consequently we cannot know with certainty whether the increased serum total CPK and CPK MB isoenzyme activities observed in hypothermia represent a loss of enzyme activity from irreversibly damaged cells or a transient phenomenon related to reversible muscle injury In either case the appearance of the CPK MB isoenzyme in the serum of patients with profound hypothermia does not necessarily indicate the occurrence of the discrete acute myocardial infarction Alternatively in the absence of other clinical criteria of infarction the presence of the MB isoenzyme of CPK in serum of patients with hypothermia probably indicates participation of myocardium in a diffuse ischemic process This process may occur either during hypothermia with local enzyme sequestration and release during rewarming or during rewarming itself The animal data would support either view

Summary

Six patients with severe medical disorders and profound hypothermia are presented who had elevated total serum creatine phosphokinase (CPK) and CPK MB isoenzyme activity without clinical or postmortem evidence of acute myocardial infarction Experiments in dogs indicate that hypothermia reduces total CPK activity in both striated and myocardial muscle resulting in increased serum enzyme activity These data suggest that profound hypothermia may result in diffuse striated and cardiac muscle cellular injury without evidence of discrete infarction with consequent release of CPK MB isoenzyme into serum

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Case reports

The prominent electrocardiographic conduction aspects of hypokalemia in a patient with periodic paralysis

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The classical electrocardiographic features of hypokalemia have been extensively studied and are presently quite well known However there appears to be less familiarity with the role of hypokalemia alone in the causation of cardiac arrythmias atrioventricular (AV) and intraventricular conduction disturbances (IVCD) Arrythmias include sinus bradycardia supraventricular and ventricular premature contractions in begeminal form with short coupling intervals atrial flutter atrial tachycardia with block atrioventricular dissociation (AVD) ventricular tachycardia (VT) and fibrillation and sudden death

The existence and frequency of AV and IVCD in hypokalemia continues to be controversial First degree and second degree Wenckebach AV block have occasionally been observed [3] Chung believes that clinical AV block other than a prolonged P R interval is rare and an IVCD is extremely unusual Fowler notes that ordinarily hypokalemia produces little or no change in the P R and QRS intervals Fisch [1] states in recent reviews that in contrast with experimental hypokalemia prolongation of the P R interval in the clinical setting is rare and that examination of large numbers of electrocardiograms (ECGs) of patients with low serum potassium (K) by numerous investigators reveals no statistically significant prolongation of the P R and QRS intervals Noteworthily moderate widening and bizarreness of the QRS complex has only rarely been observed in pure severe hypokalemia [1] This communication depicts prominent electrocardiographic features of severe hypokalemia observed in a Negro male presenting with hypokalemic periodic paralysis (HPP)

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Case report

This 37 year-old Negro Puerto Rican male enjoyed good health until 19,4 when he had an episode of transient paraparesis He recovered spontaneously and was well for the following two years except for myalgias that appeared after strenous exercise On April 22 1976 he engaged in unusually heavy labor and in the evening he ate a large amount of cake and ice cream On the following day he awoke with weakness of the legs and was taken to another hospital where cerebro spinal fluid analysis was normal An infusion of 5 per cent dextrose in water (D/W) was started There was progression of symptoms as jud ed by the development of flaccid quadriplegia and dysphagia with retention of secretions and difficult breathing He was then transferred to our hospital The remainder of the history and family history were negative On admission April 24 the physical examination was normal except for an irregular pulse of 96 and absent deep tendon reflexes He was immediately intubated and assisted ventilation was started The 6 A M serum potassium was 1 3 mEq /L. while serum sodium chloride and CO content were normal Blood gas determinations revealed the following PO = 65 13 mm. Hg pCO = 21 23 mm Hg HCO = 11 15 mEq /L and pH = 7 32 7 43 these are at variance with the CO content value Spontaneously eight hours later the patient could move all extremities and the ECG and serum electrolytes had reverted to normal Potassium administration was begun twelve hours after admission when the results of the initial electrolytes became available Unfortunately the patient received some 4 liters of D/W or dextrose in normal saline during the first 24 hours Subsequent studies showed a normal hemogram urinalysis, blood chemistry profile serum electro

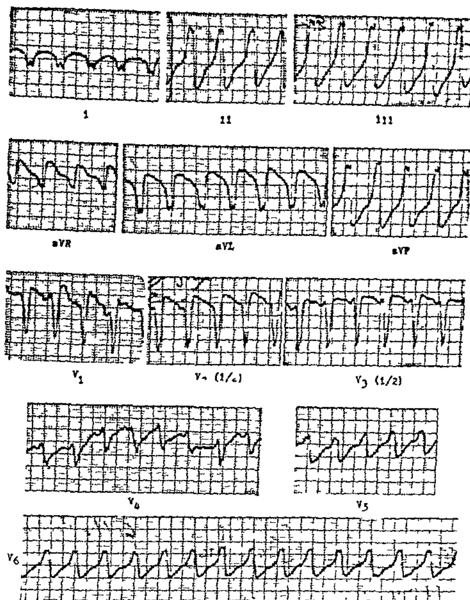


Fig 1 ECG 4 24 76 3 A M Rate = 120 P R interval = 0 11 0 12 sec QRS interval = 0 20 sec (total 0 40 sec) QT (QU) interval = 0 40 sec axis + 110 degrees Probable sinus tachycardia All complexes are nondiscript but the QRS complexes are extremely wide. The ST segments are depressed in Leads II III aV_F V and elevated in Leads I aV_R aV_L V The T and U waves are not identified See text

lytes chest roentgenogram esophagram barium enema sigmoidoscopy electroencephalogram electromyogram nerve conduction velocity serum aldolase pulmonary function studies serum thyroxine and cortisol and 24 hour urine studies for 17 hydroxy and ketosteroids sodium potassium bicarbonate and creatinine clearance The serum and urinary aldosterone values while on a regular diet were normal The sodium and potassium content of muscle after recovery were 71 6 and 62 1 mEq /L respectively these represent an increase of muscle sodium and a marked decrease of muscle potassium Light and electron microscopy revealed minimal atrophic changes increased glycogen granules and mitochondria and vacuolizations within muscle fibers immunofluorescent examination showed faint linear staining with IgG along the interstitial spaces all consistent with periodic paralysis The patient was discharged on a low salt low carbohydrate diet and acetazolamide 250 mg twice daily

Interpretation of the electrocardiograms The ECG s were all taken during the same day (within 16-½ hours of each other) (See legends to illustrations) Fig 1 tracing was obtained in the Emergency Room on arrival Unfortunately no serum potassium was drawn to correspond to this interesting ECG when it was most likely lower than 1.3 mEq /L. All the electrocardiographic complexes were nondescript the QRS complexes were markedly widened (at least 0 20 sec) the ST segments were either depressed or elevated but neither junction J nor T and U waves could be delineated If the small rounded waves preceding the QRS complexes in Lead V are indeed P waves there is apparently shortening of the *P R* interval and an early QRS in the last complex (cut off) of this strip VT or accelerated idioventricular rhythm are considered less likely

Fig 2 ECG s were taken 3 hours later when the serum potassium was 1 3 mEq /L. Notable changes have transpired in that the QRS complexes have narrowed to 0 10 sec duration and the ST segments T U and P waves are now identifiable The ST segments are depressed in many leads *U* waves are prominent and are somewhat fused to the T waves. The first beat in *Lead III* is probably a junctional escape beat (JFB) with aberration This tracing *2A* is suggestive of the

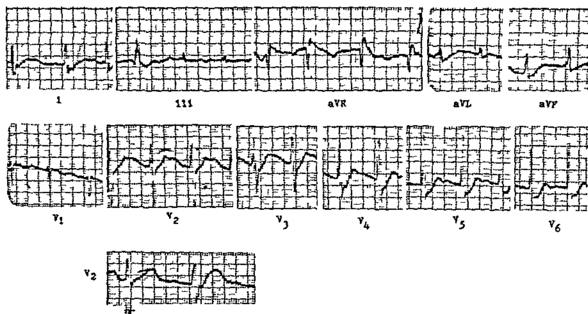


Fig 2A ECG 6 A M QRS interval = 0 10 sec QT = 0 40 sec Q U = 0 54 sec axis + 45 degrees Depressed ST segments in Leads I II aV aV V and elevated in aV U waves are prominent The T and U waves appear to be fused but are sufficiently separated in the precordial leads to be identified. Th lower V lead shows a P wave separated from the fused TU waves

usual hypokalemia pattern Fig 2*B* however reveals striking complex alterations in AV conduction Atypical Type 1 second-degree Wenckebach AV block develops which appears to be unlike variations previously described In strip *a* of Fig 2*B* the P R interval of the second Wenckebach group increases in the third and fourth beats and then remains the same (0 24 sec) The P R of the first beat of the last group does not shorten but shortening occurs in the third beat The R R interval remains about the same Strip *b* of Fig ?*B* shows the atrial rhythm remaining slightly unstable and irregular The P R intervals vary shortening and then lengthening markedly before the blocked beat so do the R R intervals vary lengthening and then shortening The maximally conducted P R interval is quite long 0 66 sec The blocked beat initiates a brief period of AVD in the middle portion of the lower strip with an unstable pathological accelerated junctional rhythm (rate of 88 to 97) perhaps due to concealed antegrade discharge of the junctional pacemaker cell The acceleration may be due to phase 4 depolarization from the hypokalemia. Another possibility in the lower strip of Fig 2*B b* is that all the P s are conducted except for $P_{..}$ P conducting to the eighth QRS complex In strip *c* of Fig ?*B* the first group the P R intervals increase and then decrease with the first P R (0 1 sec) being slightly less than that just prior to the pause (0 23 sec) The R R is variable but the last R R is less than the first R R interval. The Wenckebach sequence ends in a blocked P (P) pause followed by a JEB (R) with aberration perhaps due to a fascicular beat or to phase 4 depolarization[24] the ensuing pause consists of a concealed conducted atrial impulse (P) allowing conduction of the next sinus impulse introducing another Wenckebach period, the first P R of which i 0 18 sec The last P R is longer and the last R R narrower than those beginning the sequence The R P (R to blocked P) and R P (R to concealed conducted P) equals 0 45 and 0 64 sec., respectively The P R (conducted *P* to escape beat) interval is considerably greater 1 44 sec than the $P_{..}$ R (concealed P to the next conducted R) interval of 0.88 sec In *strip d of Fig 2B* the *P R* interval shortens prior to the pause and subsequent JEB with aberration Supernormal conduction (SNC) or a delay at two sites may explain this [n] The R P is 0 45 sec The P R intervals preceding the JEB s in trips *c* and *d* are 0 ?3 sec. The second QRS complex of strip *e* is probably an aberrant JEB while the last beat is conducted with a markedly prolonged P R interval (0 66 sec) In strip *f* of Fig 2*B* two Wenckebach periods are present The P R in the first ranges from 0 16 to 0 58 sec., suddenly prolonging before the blocked P the R R cycle narrows remains the same and then lengthens markedly before the block. The QRS of this prolonged conducted P wave the subsequent JEB (dissociated from P) and subsequently prolonged conducted *QRS complex* (P R of 0 56 sec)—the sixth to eighth QRS complexes—are aberrantly conducted. The seventh QRS complex is probably an accelerated JEB —actually the longer *the P R* interval, the closer the R of the conducted beat comes to the R of the escape beat—less likely it is conducted with a skipped P wave (the second P wave before the QRS complex being the conducted sinus impulse *rather than* the immediately preceding P) Again concealed conduction ensues in the tenth P and allows atrial conduction to manife t introducing the second sequence the last beat of which follows delayed AV conduction (0 64 sec) after the first three beats with essentially constant P R *and* R R intervals. Before the JEB the R P is 0 10 sec and the penultimate R P interval is 0 43 sec The R P intervals preceding the prolonged conducted beats (R P) are 0 43 0 60 and 0 46 sec respectively The P R intervals before the first and last prolonged conducted beats are 0.25 and 0.22 sec The R P before the conducted beats in strip *c* and strip *f* of Fig 2*B* are 0 64 and 0 15 sec., respectively

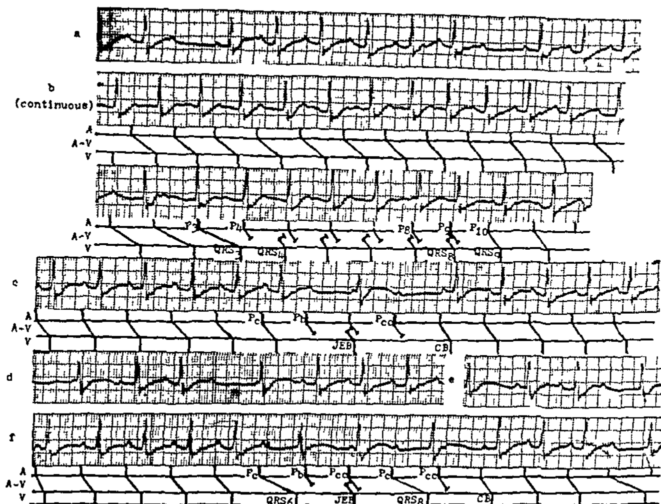


Fig 2B Lead II rhythm strips 6 A M *a* to *f* See text *a* AR = 85 90 Slight sinus arrhythmia P R intervals = 0 20 0 24 sec Atypical Wenckebach periods Concealed conduction *b* AR = 84 98 Sinus arrhythmia Atypial type I second degree AV block with markedly prolonged AV conduction followed by AV dissociation and an unstable accelerated junctional rhythm in the midportion of the lower strip Concealed conduction *c* AR = 85 88 Atypical type 1 second degree AV block A JEB with aberration follows the first Wenckebach sequence The second sequence results from a conducted atrial impulse aided by concealed conduction of the prior atrial impulse *d* Supernormal conduction may explain the slight P R shortening before the pause *e* The second ventricular beat is aberrant and is probably a JEB while the last beat conducts at a prolonged P R interval of 0 66 sec *f* AR = 83 88 Atypical Wenckebach block JEB with aberration Concealed conduction allows AV conduction to culminate *CB* = conducted beat *JEB* = junctional escape beat P_b = blocked atrial impulse P = conducted atrial impulse P = concealed atrial impulse

(the R P interval is anticipated to be longer than the R P_b and thus partial penetration occurs) The P R distances are the same (P R longer R R of JEB shorter) the P subsequent R interval is greater than the P R interval so a conducted beat occurs The P R intervals are 1 24 and 0 88 sec The atrial impulses in pauses of Wenckebach sequences have been considered to be either conducted or blocked with JEBs. [32] However the brilliant analyses of Langendorf and Pick have offered methods for distinguishing escape beats following blocked atrial impulses from conducted beats permitted by concealed atrial impulses.

Fig 3 ECG taken six hours later (potassium of 4 0 mEq /L one-half hour prior) is compatible with typical hypokalemia showing slight ST segment sagging and prominent U waves the QRS width is normal

A tracing *Fig 4 done* 7½ hours later was normal

Discussion

Cardiac arrhythmias such as multifocal ventricular ectopic beats and VT and/or conduction disturbances have occurred during or between attacks of the various types (hyper normo and hypokalemic) of periodic paralysis [33 35]

Conduction disturbances in periodic paralysis and hypokalemia In 1941 Stoll and Nisnewitz[36] observed a patient with HPP who demonstrated P R interval prolongation and dropped beats Atropine normalized the P R interval and raised the T wave suggesting increased vagal tone during the attacks [36] Renal hypokalemia patients may show first and second degree AV block [ ] Other cases of HPP have shown hypertension bradycardia cardiomegaly atrial fibrillation (Af) ST and T abnormalities QT prolongation and marked first and both types of second-degree AV block during spontaneous (potassium of 1 6 mEq /L) and induced attacks [3] The latter

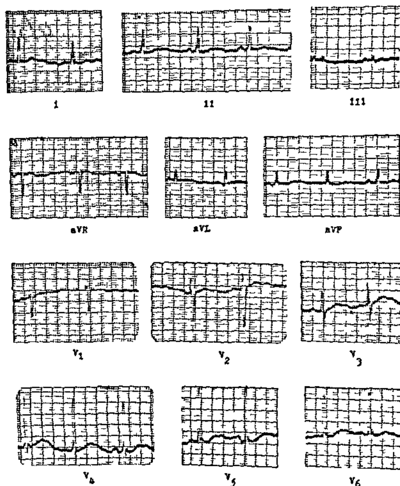


Fig 3 ECG 12 noon Rate = 62 P R = 0 16 sec QRS = 0 08 sec Q T = 0 42 sec Q U = 0 50-0 55 sec axis + 30 degrees Prominent U waves (1 mm height) but the T/U ratio = 1 or greater Slight ST segment sagging

investigators[5,7] suggested as causative a combined transient change in the conducting fibers from hypokalemia and augmented thyroxine Another case demonstrated the usual electrocardiographic pattern but the serum potassium was never lower than 3 2 mEq /L [3]

Stewart and colleagues in 1940 were probably the first to record in the English language a case of familial periodic paralysis (FPP) and hypokalemia depicting QRS complex widening A 19 year old male s ECG (with half normal serum potassium) showed during an attack of paralysis P R QRS (0 12 to 20 sec wide depending upon the placement of junction J and the QRS was of right bundle branch block type) and QT interval prolongation which corrected with potassium chloride (KCl) and subsidence of the attack They cited one similar case from the German literature Brown and associates cited another case of FPP (their Fig 3) in whom the ECG showed slight impairment of intraventricular conduction (QRS of 0 11 to 0 12 sec) which was attributed to coronary heart disease Transient widening and splintering of QRS complexes have rarely been observed in hypokalemic diabetic acidosis In Henderson s two patients the QRS width was up to 0 14 sec in the lateral precordial leads (normal width in other leads) in one female with Af and ranged from 0 16 to 0 20 sec in the chest leads (normal in bipolar leads) of the second female whose later tracing had narrower complexes with an even lower potassium level Both of these patients died A possible role of intracellular potassium was considered as there was no correlation between the serum potassium and the degree of cardiographic abnormality Surawicz reported one case with a slur at the foot of the descending limb of the R wave and a QRS width

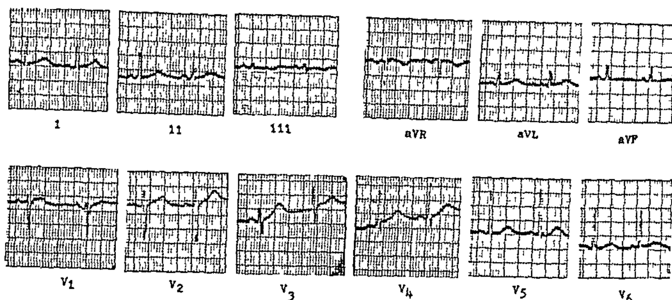


Fig 4 ECG 7 30 P M Rate = 80 P R = 0 13 sec QRS = 0 08 sec Q T = 0 40 sec axis + 35 degrees Normal electrocardiogram

of about 0 12 sec However, he believed these were rare in hypokalemia and seemed to appear only at very low potassium levels or in combination with other factors such as acidosis[47] Sarma s two cases[48] of hypochloremic alkalosis and hypokalemia had mild to moderate increases in width (about 0 11 sec) and amplitude of the QRS complexes and in the P R length Recent reviews[4] and textbooks of cardiology[51 53] recognize occasional AV conduction defects, but only slight diffuse QRS widening without change in configuration in advanced hypokalemia the magnitude of these is relatively small and can be recognized only in serial tracings since the measured intervals remain within normal limits[1]

Probably the most striking case ever published and that most resembling ours is the 6 year old boy with cystinosis, severe metabolic imbalance and hypokalemia (1 6 mEq /L) reported by Cherry and Surawicz[15] This patient s ECG revealed uniform QRS widening (0 14 to 0 18 sec) associated with first and second degree Wenckebach AV block and multiple ectopic, fusion, and escape beats during intravenous administration of glucose in salt solution After giving potassium chloride intravenously a short ST segment followed by a T wave merged to the U wave was interposed followed by disappearance of the AV block and narrowing of the QRS width to normal Initial masking of the characteristic features of hypokalemia was attributed to the tachycardia and IVCD the former fusing the T with the U and P waves while the secondary ST and T changes of the latter directed oppositely to the wide terminal portion of the QRS counteracts the primary ST T changes of hypokalemia A long R R interval separating the T from the P, and the potassium chloride infusion unmasked the true nature of the condition, in spite of its mimicry of a hyperkalemic pattern The Lead V_3 QRS duration was only 0 10 sec and there was a short ST segment visible These investigations and the studies of Surawicz[54] indicating that the short slurred segment following the QRS corresponds to the shortened initial phase of repolarization (phase 2), and previously published studies of severe hypokalemia with widening affecting mainly the terminal portion of the QRS making distinction between a terminal slur of the S wave or a short ST segment very difficult were emphasized by the authors[15] This dilemma is also recognized in our case These investigators believed that even if the atypical short ST segment were not incorporated into the QRS the latter still showed generalized widening as it narrowed from 0 10 to 0 06 sec after administration of potassium

In Conn s case[55] (potassium of 2 5 mEq /L) there was P R prolongation but no or very minimal QRS widening Attacks of paralysis were induced but electrocardiographic changes did not correlate with the serum potassium levels even down to a potassium level of 1 48 mEq /l In a 30 year old female without heart disease right bundle branch block was observed during induced hypokalemia In the presence of orthograde blocking the impulses entered the right bundle branch in a retrograde manner the velocity of

retrograde activation being dependent upon heart rate and seen as a spike after the ventricular potentials or His bundle recordings[56]

Experimental studies—hypokalemia and conduction defects In contrast to human clinical experience studies in experimental animals with hypokalemia reveal delay and block of AV transmission in pigs fed a low potassium diet and in the isolated frog turtle and rabbit heart when exposed to low potassium perfusions glucose and insulin infusions and low potassium dialysis can induce AV conduction disturbances in dogs Intraventricular conduction delay is less pronounced but has been described in the rabbit turtle and dog and in calves fed a potassium free diet[6 13 47 5 57 63]

Surawicz Gettes and associates [58] found that perfusing isolated rabbit hearts with low potassium solutions caused a prolonged phase 3 and shorter phase 2 and an increased amplitude duration and upstroke velocity of the action potential (AP) reflected in a progressively diffuse widening and augmented amplitude of the QRS complex without a change in shape This slowed intraventricular conduction velocity was attributed to hyperpolarization—a decreased resting membrane potential (RMP) Sinus or junctional bradycardias with increases in P R and R P intervals developed followed by more advanced AV conduction defects such as 2 1 Wenckebach and complete AV blocks These changes reverted to normal on infusing Krebs Henselet solution

Paes de Carvalho and Langan observed impaired AV nodal transmission and block in the isolated intact Langendorff perfused rabbit heart when the potassium fell below 2 to 2 7 mM and variable AV block with irreversible damage to propagation at levels less than 1 mM There was a slight tendency to QRS prolongation and the H V interval lengthened minimally AV conduction usually corrected on raising serum potassium levels A decreased AP amplitude and rate of depolarization of AV nodal fibers depressing intranodal conduction and aggravating Type 1 block and enhancing diastolic depolarization of His Purkinje cells was found by Watanabe[62] Potassium administration may shorten the P R interval in hypokalemic patients however in others AV propagation may improve on lowering the serum potassium

Pathophysiology The mechanism for transmission delay in hypokalemia has not been clarified but may involve one or more of the following (1) hyperpolarization (more negative RMP) of the myocardial cell in diastole requiring a stronger stimulus to bring the transmembrane potential to threshold potential (TP) (2) excitation of the cell before complete repolarization producing a slower upstroke of the AP leading to slowed rates of depolarization and wider QRS complexes (3) the greater sensitivity to vagal stimulation Re entry and automaticity from augmented phase 4 depolarization enhance arrythmias [6 10 1 2 5 5 58]

Although controversial the ECG appears to reflect extracellular potassium and the myocardial cell membrane potassium gradient[5] [65] This is supported by the observation that the intracellular concentration of potassium was not significantly different in hearts perfused with low normal and high concentrations of potassium[5] and the fact that in FPP the ECG may reflect rapidly changing plasma potassium levels the electrocardiographic changes occurring during an attack of paralysis are those characteristic of hypokalemia but more severe than those seen in normal persons at comparable levels of serum potassium Serum potassium falls but the status of muscle potassium is not settled[0 66] In our patient muscle potassium was very low Authorities agree that the actual level of serum potassium during an attack whether or not accompanied by an arrythmia is unlikely to be crucial[6] Also these electrocardiographic changes are believed to be due to the electrophysiological alterations rather than to the anatomical lesions of hypokalemia[5 5]

The initial ECG (Fig 1) shows ST elevations in Leads I aV_R aV_L and $V_{1\ 3}$ a rare finding in hypokalemia[68] This tracing resembles that of hyperkalemia more than that of severe hypokalemia an observation appreciated once before[15] and the AV block and ST segment depression have been said to be the same in these conditions except for low T waves in the latter

Originally Surawicz and colleagues[47 5] interpreted the QRS alteration as a slurred terminal portion of the depolarization process in each heart muscle element Later works view the ventricular complex in advanced hypokalemia as being diffusely widened from an IVCD due to generalized slowing of propagation in the ventricular myocardium and/or Purkinje fibers and not

from a focal block in a bundle branch[3, 4, 15, 57]

So as reviewed studies are inconsistent some purporting that clinical hypokalemia never produces any significant consistent QRS complex widening,[6, 13, 14] others accepting slight widening (0 01 to 0 03 sec),[3, 4, 11, 47, 50, 51] or more pronounced widening particularly in children,[1, 4, 15, 5] as well as AV conduction defects

Atrioventricular conduction defects Moreover the AV conduction abnormalities in our patient are most interesting Atypical forms of Wenckebach block are present,[16, 5] and without His bundle recordings these can offer difficulty in recognizing the nonconducted atrial impulse Various manifestations of concealed conduction (atrial echo beat concealed AV nodal re entry, etc) and supernormal (Type A) conduction may play a critical role, the delayed JEB provides sufficient time for atrial propagation, so that in a record with unquestionable AV nodal escapes contrary to the rule, the longer ventricular cycles terminate with conducted beats while shorter cycles terminate with JEB's Langendorf and Pick [71] state that if the distance between the concealed atrial impulse (P_c) (the blocked P following P) and the subsequent R (P R) approaches the established conducted atrial impulse to escape distance (P R) the R represents an escape beat if P R is considerably shorter, then the beat terminating the pause engendered by the concealed P is a conducted beat [11, 1]

Concealed and supernormal conduction have been induced experimentally in dogs from potassium induced depression of AV conduction [9] Changing levels of serum potassium (2 7 mM/L to hyperkalemia) experimentally have little effect on the sinoatrial node [6, 70] but a vagal effect on the AV node producing Wenckebach block may become manifest under conditions of nonresponsiveness of the former to vagal stimulation [1] Hypokalemia augments the cardiac sensitivity to vagal stimulation and this enhanced tone may induce marked sinus bradycardia and AV transmission defects,[10, 11] a mechanism perhaps of import in our patient

Aberrancy of the JEBs and the slowly conducted beats (prolonged P R intervals) manifesting late may be attributed to Mahaim fiber conduction fascicular origin from the left bundle branch phase 4 depolarization shift of the TP toward zero, concealed escapes and hypopolarization [6, 7, 7, 74] The studies of Singer and colleagues [7] revealed that the development of phase 4 depolarization with a decrease in potassium conductance was facilitated by lowering the concentration of potassium in the Tyrode solution They believed that such reduction in diastolic potential could lead in the intact heart to widespread involvement of the Purkinje system producing SNC, aberrancy of JEB's AV block bundle branch block, and intraventricular block of diffuse and nonspecific pattern

Although ventricular arrhythmias with conspicuous QRS widening and second degree sinoatrial and AV nodal block have been observed previously [1, 5, 7] as far as we can determine our patient with periodic paralysis and severe hypokalemia demonstrates the most striking alterations of the QRST complexes and AV conduction that have been documented in these conditions

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Isolated T wave alternans

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Alberto Periz M D
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Barcelona Spain

Isolated T wave alternans is characterized by changes in contour amplitude or polarity of the T or T U wave appearing with regular rhythmicity usually every other complex unaccompanied by any discernible modification of the QRS wave or gross changes in the cycle length

The phenomenon was described by Mines in 1913 and the first clinical example was apparently recognized by Padilla and Cossio in 1931 Occasional mention had been made of the transient postextrasystolic variety After the advent of the precordial leads a complete electrocardiographic tracing was published by Kimura and associates[3] in 1963 Eleven cases have been described in the literature associated with acquired repolarization disturbances [2] and 13 more were recently recognized by Schwartz and colleagues who examined 28 reported cases of the Romano Ward syndrome Its true incidence however as well as the clinical meaning and mechanisms involved still remain obscure

Among other factors low serum calcium level may play a role in the production of the T wave alternans as suggested by Doherty and co workers and by Kimura and associates[3] It is the purpose of this report to review briefly the literature and present two observations that give additional support to their hypothesis

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Case reports

Case 1 A 16-year-old male patient entered the hospital presenting with acute glomerulonephritis hypertension and left heart failure Physical examination disclosed a regular rhythm at 156 beats per minute a blood pressure of 165/115 mm Hg and a respiratory rate of ?3 Weight was 28 kilograms Pulmonary rales were present The hematocrit was 37 per cent the hemoglobine 1? Gm and the urea nitrogen 64 mg per 100 ml The sodium was 137 mEq the potassium 5 mEq the chloride 106 mEq and the carbon dioxide 17 6 mEq per liter The pH was 7.38 and the pCO was 26 mm Hg The urine gave a positive test for protein and its density was 1010 Diuresis measured 690 ml the first ?4 hours

Treatment during the first two days included a total dosage of 0 6 mg. of intravenous Cedilanid Furosemide 10 mg intravenously and reserpine 0 5 mg intramuscularly were given every ei ht hours The heart rate lowered to 40 beats per minute the third day the blood pressure to 115/50 mm Hg and the respiratory rate to 28 per minute Diuresis increased to 1,200 ml. The electrocardiogram and the vectocardiogram recorded showed a 2 1 and occasionally a 3 1 T wave alternans and a few ventricular premature beats (Figs. 1 and ?) Striking changes of repolarization were very evident in the left precordial leads. T wave measured 0 75 mV negative and the corrected QT interval 0 75 sec in Lead V changing alternatively to 0 3 mV and 0 65 sec Physical examination failed to disclose pulse alternans The urea nitrogen was 3? mg the serum proteins 5 4 mg and the calcium 8 2 mg per 100 ml The sodium was 158 mEq the potassium 3 6 mEq the chloride 108 mEq and the carbon dioxide ?5 mEq per liter The pH was 7 4? and the pCO 32 mm Hg To control the bradycardia 0 5 mg of oxyphenonium bromide was administered intramuscularly and the T wave alternans ceased at a heart rate of 50 beats per minute

Case 2 A 60 year-old woman was admitted to the emergency room after two days of diarrhea abdominal cramps vomiting and fever She had had a goiter operation two years before and followed irregular treatment for hypocalcemic tetany

Physical examination showed poor general condition Temperature was 39 C., pulse 93 beats per minute and blood

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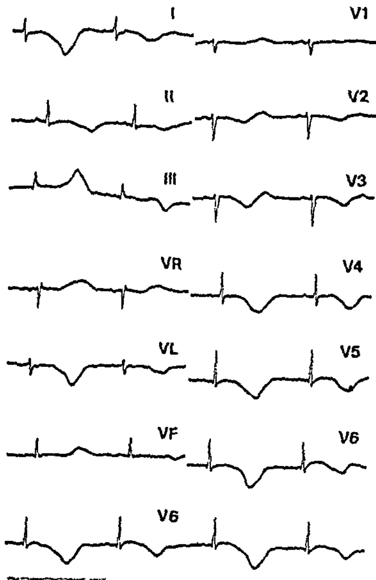


Fig 1 Electrocardiogram of Case I showing the T wave alternans See text for discussion

pressure 80/40 mm Hg Chest x rays were normal Laboratory findings included a hematocrit of 43 per cent and a white blood cell count of 13 000 per cubic millimeter Blood urea nitrogen was 90 mg and glucose was 167 mg per 100 ml Serum sodium was 137 mEq and potassium 2 2 mEq per liter The electrocardiogram demonstrated T wave alternans

Acute gastroenteritis was diagnosed and treated with antibiotics fluid replacement and infusion of 60 mEq of potassium. Twelve hours later the blood pressure was 100/50 mm Hg the temperature 39 5 C and signs of tetany were elicited Laboratory data showed a hematocrit of 38 per cent a urea nitrogen of 80 mg glucose of 145 mg serum proteins of 6 6 Cm and calcium of 3 mg per 100 ml Serum sodium was 139 mEq potassium 3 mEq and carbon dioxide 21 mEq per liter The pH was 7 45 and the pCO 30 mm Hg Base excess was 5 6 The electrocardiogram was similar to the previous one and showed again T wave alternans (Fig 3) There was a sinus rhythm at a rate of 100 per minute and a left bundle branch block pattern. The *QT interval measured 0 72 sec* and 0 67 sec alternately Carotid sinus stimulation on both sides was applied and followed by momentary interruption of the alternans (Fig 4) that was abolished with the infusion of 20 ml of a 10 per cent solution of calcium *glucorate* the heart rate rising to 110 beats per minute and the blood pressure to 115/80 mm Hg During the next hours recurrence of the alternans and frequent episodes of ventricular fibrillation ensued requiring electrical cardioversion on two occasions Two hours later serum calcium level was 3 6 mg per 100 ml and the potassium was 2 4 mEq per liter The ventricular instability was permanently abolished after additional infusions of 60 ml of the calcium solution were given in six hours raising the calcium level to 5 8 mg per 100 ml while the potassium concentration still was 2 5 mEq per liter Oral treatment with calcium and potassium was followed by normalization of the electrolite concentration and the ventricular repolarization in a week The patient had a complete recovery

Discussion

Electrocardiographic aspects The electrocardiograms of our two cases and the six collected from the literature with precordial leads[7, 9, 10, 12] have the following features in common

1 The left precordial leads show a giant negative T wave, its voltage ranging between 0 75 and 2 2 mV negative, with an average of 1 2 mV, that reduced the amplitude in the following beat by a decrement that ranged between 0 35 and 3 5 mV (mean, 1 16 mV) In three cases[7, 9] it was large enough to change its polarity in one or more leads The horizontal axis of the more aberrant of the T waves was located in the right anterior quadrant, except in the case reported by Wellens[10] and in our second case, with the left bundle branch block

2 The corrected QT intervals were severely prolonged the longest duration measuring between 0 62 and 1 09 sec (mean, 0 76 sec)

3 The QT interval shortened every other beat by an amount that varied in the different cases between 0 28 and 0 05 sec (mean 0 10 sec) Due to their constant association with the T wave alternans the long QT and the QT alternans probably should be considered genuine components of the electrocardiographic picture In fact, according to current views of the T wave electrogenesis,[14] the changes in depth could be explained by non homogeneous changes in duration of the recovery

4 An increased tendency to ventricular instability manifested by ventricular premature beats and ventricular fibrillation[9, 11, 12] well documented in Case 2 further emphasizes the electrocardiogrpahic similarity with the congenital long QT syndrome of the Romano Ward type where the episodes of T wave alternans and ventricular

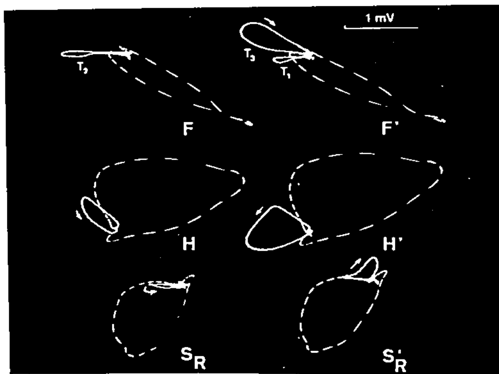


Fig 2 Vectocardiogram of Case 1 (Frank system) recorded at the same time as the electrocardiogram of *Fig 1* F H S and F' H and S Frontal horizontal and right sagittal projections corresponding to the two different alternant T waves T and T two different T loops of the main 2 1 alternant sequence T intermediate T loop of a 3 1 sequence See text for discussion



Fig 3 Electrocardiogram of Case 2 during T wave alternans See text for discussion

fibrillation are not uncommon[2] The instability has been related to the severe prolongation of the QT interval and the temporal dispersion of the repolarization

It has been suggested that the repolarization alternans may represent changes in the U rather than in the T wave[3] [11] but this possibility seems unlikely since the majority of the tracings show early as well as late repolarization changes[15] The vectocardiogram showing also a better spatial display of the depolarization than the electrocardiogram seems to ratify that the T wave changes are independent of the ventricular activation (Fig 2) The concept of isolated

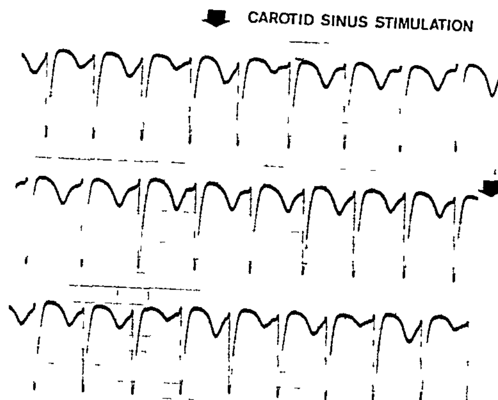


Fig 4 Case 2 Continuous tracing of Lead V_2 during carotid sinus stimulation showing the interruption of the T wave alternans *Arrows* point to the beginning and the end of the stimulation

Table I Published cases of T wave alternans

Authors	*Year*	*Age*	*Sex*	*Ca*	*K*	*Mg*	*HR*	*HD HF*	*VF*
1 Padilla and Cossio[2]	1931	60	M	–	–	–	54	HF	–*
2 Lian et al	1931	25	M	–	–	–	43	HF	–
3 Enselberg	1952	50		–	–	–	107	HD	–*
4 Hubbard et al	1956	24	F	–	–	–	88	HD	–
5 Kimura et al	1968	71	F	7 8	3 6	–	88	HD	–
6 Rickets et al	1969	35	M	–	4 1	0 9	130	HF	–
7 Dolara and Pozzi	1971	57	M	8 8	3 2	–	125	–	–
8 Fish	1971	80	M	–	–	–	82	HD	VF
9 Wellens	1972	49	F	10 2	4 8	–	64	HD	–
10 Bashure et al	1973	36	F	7 5		1 3	77	–	VF
11 Luomanmàki et al [2]	1975	63	F	8 1	3 1	1 14	46	HF	VF
12 Case 1	1976	16	M	8 2	3 6	–	44	HF	–
13 Case 2	1976	45	F	3	2 8	–	84	–	VF

Ca = Total serum calcium concentration in mg per 100 ml HR = heart rate during T wave alternans HD = heart disease HF = heart failure K = potassium concentration in mEq /liter Mg = magnesium concentration in mg per 100 ml VF = episodes of ventricular fibrillation

* = Electrocardiographic recording with precordial leads unavailable

alternans depends essentially on the inspection of the tracings[9] and theoretically even minor changes in depolarization could explain very apparent T wave alterations

Clinical setting and etiology Aside from the T wave alternans that appear in the congenital long QT syndrome and may be considered its congenital counterpart the acquired alternans has been observed in the following clinical situations (1) after rapid ACD blood transfusion during surgical hypothermia[6, 13] (2) in patients with hypertensive heart disease and renal failure[2, 5, 9] associated with mild hypocalcemia[5] as in Case 1 (3) in severe pancreatic disease with shock renal failure, and low serum calcium and potassium[8], (4) in severe chronic alcoholic ingestion with heart failure due to cardiomyopathy[7, 12] or tetany[11] where T alternans was associated with hypomagnesemia and corrected by magnesium infusion and (5) after persistent supraventricular tachycardia in a patient with heart failure treated with quinidine and cardioversion[10] Our Case 2 describes a new clinical condition with severe hypocalcemia due to parathyroid deficiency

The possibility that calcium may have some bearing in the etiology of the T wave alternans is based mainly on its clinical observation after

ACD blood transfusion[6,13] and during experimental hypocalcemia[13,5,16] This view appears to be supported by the finding of mild hypocalcemia and a clinical setting compatible with calcium imbalance in the majority of the cases reviewed[1,8,11,12] (Table I) although the pertinent information about the ionized serum calcium level is lacking The severe hypocalcemia documented in Case 2 and the correction of the alternans after calcium infusion give additional evidence in favor of the causative role of the low calcium concentration

Hypomagnesemia has also been implicated (Table I) and since ionized serum calcium and magnesium concentrations are closely related it may be that their effects are mediated by a common mechanism In addition severe heart disease was a very common finding (Table I) absent only in Case 2 and in two previous observations [1]

The alternans was induced or intensified by deep inspiration[3] changes from recumbent to upright position or by a sudden increase in the heart rate and it was transiently suppressed in our case by carotid sinus stimulation suggesting its interval dependence and/or the participation of an autonomic nervous system mechanism in eliciting alternans as pointed out by Schwartz and colleagues[2] On the contrary the alternans was present in some cases (Table I) at low heart rates as in Case 1 where it was shown to disappear when the rate increased by the action of a vagolytic agent In view of the clinical findings it does not seem unreasonable to suspect that other factors known to prolong the QT such as hypothermia bradycardia or quinidine may have some facilitating effect

Mechanism The QT changes underlined are consistent with the hypothesis that the T wave alternans may be the electrocardiographic manifestation of the transmembrane action potential alternans. The alternation limited to rate and duration of the repolarization affecting mainly the pahse 2 is easily induced in the isolated muscle strip preparations[5,1] and shown to be influenced among other factors by the stimulation rate and the calcium concentration of the perfusion bath It has been interpreted as due to an alteration of the calcium transport mechanisms of the cell membranes[1]

Despite the apparently constant association of electrical and mechanical alternans in experimental studies[15,16,18,19] alternation of the systemic pressure has not been observed in man[5,7,9,10]

Summary

Two patients with isolated T wave alternans are reported with their vectocardiograms their response to carotid sinus stimulation and the response to calcium infusion in one of them with documented severe hypocalcemia Eleven cases of the literature are briefly reviewed

The alternans of the T wave appears with severe QT prolongation QT alternans and an increased tendency to ventricular fibrillation The findings are consistent with the hypothesis that T wave alternans may be the electrocardiographic manifestation of the transmembrane action potential alternans and could be related in some cases to hypocalcemia

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Clinical, biochemical and pathological features of low renin ("primary") hyperaldosteronism

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Some twenty years ago Conn[1] described a patient with hypertension, neuromuscular symptoms and renal potassium wasting. This was associated with increased urinary excretion of a sodium retaining hormone, subsequently shown to be aldosterone.[2] Removal of an adrenocortical adenoma resulted in a fall in blood pressure, correction of the biochemical abnormalities and disappearance of symptoms.[3] Further case reports rapidly appeared, and with increasing experience less florid cases were recognized, including asymptomatic patients and some in whom serum potassium was persistently normal.[6, 7] The disorder has been called primary hyperaldosteronism.

Diagnosis was placed on a firmer footing by the observation that plasma renin concentration[8] and plasma renin activity[9, 10] is suppressed in such patients. This distinguishes them from patients with hyperaldosteronism associated with malignant phase or renovascular hypertension—so called "secondary hyperaldosteronism"—in whom plasma renin concentration[2, 3] and plasma renin activity[1, 5] is increased. Thus the hallmarks of an aldosterone producing adenoma are hypertension, aldosterone excess and low plasma renin, commonly but not invariably with hypokalemia.[16]

Abnormalities qualitatively similar to these have also been reported in the absence of an adrenocortical tumor. The adrenal glands then show either hyperplasia of the zona glomerulosa, often with nodular changes, or a normal appearance.[17, 7] The term "primary hyperaldosteronism" seems unsatisfactory for such patients without adrenal tumors, since the adrenal changes may well be due to stimulation by an extra adrenal mechanism.[4, 2, 29] The terms "idiopathic aldosteronism"[3] and "pseudo primary aldosteronism"[6] have been applied to this group.

A few patients have been described with hypertension, aldosterone excess and low plasma renin in whom all the abnormalities were suppressed by dexamethasone.[31] Adrenal exploration in two such patients revealed adrenocortical hyperplasia. Occasional cases of hyperaldosteronism associated with adrenal carcinoma have also been reported,[35, 4] and rarely the syndrome has been associated with ovarian neoplasms.[4, 5]

In view of the variability of the disorder it may be preferable to use "low renin hyperaldosteronism" as a generic term for patients in any of the above groups, with or without an adrenocortical tumor. However, the description "primary hyperaldosteronism" is often applied to all such patients and although not strictly correct we will

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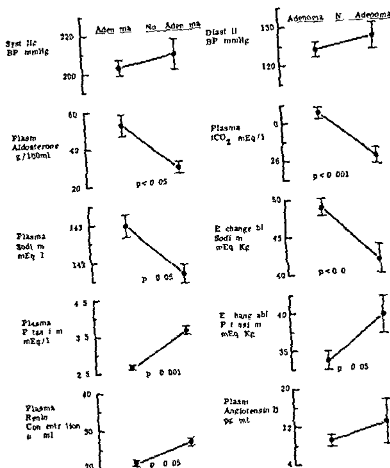


Fig 1 Comparison of variables in adenoma (N = 6?) and non adenoma (N = 17) groups Values are means ± S E M = 3? and 9 patients respectively = 29 and 8 patients respectively = 14 and 4 patients respectively

statistical calculations were made on a Hewlett Packard 9810A calculator

Clinical features

Age and sex Ages of the 136 patients ranged from 18 to 70 years (mean 46 5 years) There were 87 females (64 per cent) and 49 males (36 per cent) Of the 62 patients with a surgically proved adrenocortical adenoma 46 were female (74 per cent) while 9 of 17 proved non tumor patients were female (53 per cent)

Among those with histologically confirmed disease patients with an adrenocortical adenoma were significantly younger than those in whom no tumor was found (mean ages 42 1 and 50 7 years respectively $p < 0.01$) When the sexes were analyzed separately this age difference persisted

Symptoms A formal questionnaire on symptoms was not used and many patients were initially investigated elsewhere For these reasons a precise incidence of symptoms cannot be quoted However a review of case records revealed that of the characteristic symptoms[1,4] headache (sometimes migranous) and nocturia were common Other symptoms included muscle weakness and paresthesia (diuretic induced in at least five cases) thirst polyuria and tetany Sometimes none of the above symptoms were encountered patients then presenting either with an incidental complaint or for routine examination

Blood pressure Mean outpatient blood pressure while untreated ranged from 150/100 to 250/160 mm Hg (mean for series 205/123 ± 28/13 S D) There was no significant difference in mean blood pressure between the surgically proved tumor and non tumor groups (Fig 1)

Malignant phase hypertension Renal biopsy was undertaken in 41 cases Evidence of malig

Table I Classification of low renin ('primary') hyperaldosteronism

1	Aldosterone producing adrenocortical adenoma (Conn's syndrome)
2	Hyperplasia of the zona glomerulosa with micronodules (including a sub group with normal adrenal appearances)
Rarely	
3	Glucocorticoid–remediable hyperaldosteronism
4	Adrenocortical carcinoma
5	Hyperaldosteronism associated with ovarian tumors

also use this term A classification of low renin hyperaldosteronism is shown in Table I

This paper reviews the clinical, biochemical, and pathological features of 136 patients with low renin ('primary') hyperaldosteronism, studied over a 12 year period The published experience of other workers is also reviewed Low renin hyperaldosteronism is defined here as hypertension associated with an elevated aldosterone value on at least one occasion and with a concurrent plasma renin concentration below the mean of the normal range The condition must be clearly differentiated from low renin essential hypertension, where aldosterone is normal[46] Details of some patients have been reported elsewhere[17, 4, 28, 47, 53] The differential diagnosis[46] and treatment[54] of this condition are discussed in separate papers

Patients and methods

Clinical data All patients had a mean outpatient untreated diastolic blood pressure of 100 mm Hg or more an elevated aldosterone value (plasma aldosterone > 18 ng /100 ml or a raised aldosterone secretion rate) on at least one occasion and with a concurrent plasma renin concentration below the mean of the normal range (< 44 microunits per ml of International Standard Renin[55]) Eighty five patients were studied while taking a diet of fixed known normal intake of sodium and potassium (Na fixed for individuals at a particular point between 101 and 143 mEq /day K similarly fixed at a point between 40 and 83 mEq /day) The remainder took a normal ward diet No patient had taken diuretics, including spironolactone potassium supplements or a restricted sodium diet for at least four weeks prior to investigation Plasma cortisol concentration and/or urinary 17 oxogenic steroids and 17 oxosteroids were normal in all cases

Although plasma is preferable to serum for potassium measurement[56] plasma values were not always available and for this analysis plasma and serum estimations have both been used Forearm exercise was avoided during venepuncture, as this may falsely raise potassium values[56] Blood for measurement of plasma concentrations of renin, renin substrate angiotensin II, and aldosterone was taken between 9 00 and 10 00 hours from an arm vein, patients having remained in bed and without food since 22 00 hours on the previous evening

Since lower arterial pressures may be obtained in some patients when in the ward as compared with the outpatient clinic,[57] blood pressure readings used in this analysis were those taken in the outpatient department using a standard sphygmomanometer, with the patient seated Except for the readings reported during treatment with spironolactone, amiloride or dexamethasone, all values were obtained in the absence of hypotensive drug therapy

Laboratory techniques

Plasma electrolytes were measured by the Eppendorf flame photometer and serum electrolytes and blood urea by Auto Analyzer Plasma renin concentration was measured by the method of Brown and associates,[55] (normal range 21 to 105 microunits per ml of International Standard Renin) Plasma renin substrate was measured by the method of Tree[59] (normal range 0 45 to 1 35 μmol/l) Plasma angiotensin II concentration was measured by radioimmunoassay[60] (normal range 5 to 35 pg /ml) Plasma aldosterone concentration was measured by the double isotope derivative technique of Fraser and James[61] with minor modifications or by radioimmunoassay[6] (normal range up to 18 ng /100 ml) Gas liquid chromatography with electron capture detection[63] was used to measure plasma corticosterone (normal range 0 08 0 8 μg/100 ml) plasma 11 deoxycorticosterone (normal 2 8 16 ng /100 ml) and plasma 18 hydroxy 11-deoxycorticosterone (normal 20 to 160 ng /100 ml)

Isotope dilution was used to measure total exchangeable sodium[64] total exchangeable potassium[63, 64] extracellular fluid volume[67] total body water[6] and plasma volume[65] using the respective isotopes ^{24}Na[42] ^{42}K, ^{82}Br ^{3}H and ^{131}I

The statistical technique of quadric analysis has been reported elsewhere[21, 7] This and other

before treatment in 32 patients in the adenoma group and in nine in whom a tumor was not found Mean values were significantly higher in the former group (Fig 1)

Plasma potassium and total exchangeable potassium Mean plasma potassium concentration before treatment ranged from 1 8 to 4 6 mEq /L and was significantly lower among patients in whom an adenoma was identified, compared with those in whom a tumor was not found (Fig 1)

Plasma potassium was measured on three or more occasions in each of 121 patients Among these hypokalemia (plasma potassium < 3 7 mEq /L) was persistent in 62 (51 per cent) and intermittent in 46 (38 per cent) while in 13 (11 per cent) plasma potassium was persistently normal Hypokalemia occurred in all 62 patients with a proved adenoma and was persistent in 53 Among the 17 patients in whom a tumor was not found hypokalemia was persistent in four and intermittent in 10 but plasma potassium was persistently normal in three

Total exchangeable potassium was measured before treatment in 29 and eight patients respectively in the groups with and without an adrenocortical tumor Mean values were significantly lower in the former (Fig 1)

Plasma tCO_2 Mean plasma tCO_2 ranged from 22 0 to 37 0 mEq /L before treatment and was significantly higher among patients with a proved adenoma (Fig 1)

Blood urea Mean blood urea before treatment ranged from 18 3 to 87 5 mg per cent being raised (greater than 40 mg per cent) in 27 cases There was no significant difference in mean values between patients with a proved adenoma and those in whom an adenoma was not found There was a significant inverse correlation between preoperative blood urea concentration and the fall in both systolic and diastolic pressure after surgery There was also a significant inverse correlation between pretreatment blood urea and the fall in systolic pressure during treatment with spironolactone

Plasma renin concentration Mean individual plasma renin concentration before treatment varied from 3 2 to 56 8 microunits per ml International Renin Standard (normal 21 to 105 microunits/ml) while plasma renin was below the mean of the normal range (< 44 microunits/

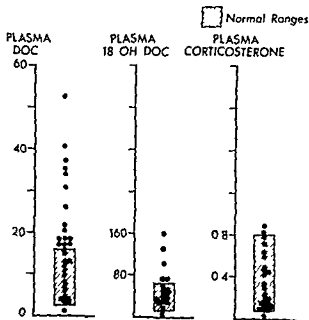


Fig 2 Plasma levels of DOC (ng /100 ml.) 18-OH DOC (ng / 100 ml.) and corticosterone (µg/100 ml) in primary hyperaldosteronism

ml.) at least once in all Values were significantly lower in the group with a proved adenoma compared with those in whom a tumor was not found (Fig 1)

Plasma renin substrate Plasma renin substrate was measured before treatment in 16 patients mean values ranged from 0 54 to 1 30 µmol/L (normal 0 45 to 1 35 µmol/L) There was no significant difference between patients with a proved adenoma and those in whom a tumor was not found

Plasma angiotensin II Plasma angiotensin II concentration was measured before treatment in 33 patients mean values varied from 4 2 to 26 0 pg /ml (normal 5 to 35 pg /ml) Although mean values were lower in patients with a surgically proven adenoma compared with those in whom a tumor was not found this difference did not reach conventional levels of statistical significance (Fig 1)

Plasma 11 deoxycorticosterone (DOC) Plasma DOC was measured in 26 patients (32 estimations) Values ranged from 1 1 to 52 5 ng /100 ml (normal 2 8 to 16 ng /100 ml) (Fig 2) Raised values were found in 13 including six of 12 patients with a proved adenoma and two of four patients in whom a tumor was not found at operation

Table II Incidence of abnormalities in plasma aldosterone potassium, and renin concentrations in 54 patients with primary hyperaldosteronism in whom plasma aldosterone was measured on two or more occasions

	Elevated plasma aldosterone	*Sub normal plasma K*	*Sub normal plasma renin*
Persistent	22	24	1
Intermittent	32	24	38
Not found	0	6	15

nant phase hypertension (fibrinoid necrosis of the renal arterioles) was found in four In two of these patients percutaneous biopsy was taken before starting treatment, while in the remaining two cases biopsy was taken at the time of operation These findings may be an underestimate of the true incidence of fibrinoid necrosis before treatment Renal biopsy is now undertaken in all cases coming to operation, but in recent years blood pressure has usually been well controlled with spironolactone, often for several months, affording time for severe renal lesions to heal In one patient renal biopsy before treatment showed fibrinoid necrosis subsequently blood pressure was well controlled with spironolactone and repeat biopsy several months later showed moderate hypertensive vascular changes only and fibrinoid necrosis was not observed

Among the four patients with histological evidence of malignant phase hypertension papilledema was observed in one associated with bilateral hemorrhages and exudates Hemorrhages and exudates without papilledema were seen in another but in the remaining two patients none of these abnormalities was observed

Vascular complications of hypertension Vascular complications of hypertension, such as stroke, myocardial infarction and angina occurred in 31 patients (22 8 per cent) In 23 cases such complications had occurred before the time of diagnosis and treatment Details of these patients and their individual lesions are given elsewhere [11]

The mean age of patients with vascular lesions was significantly greater than the mean age of those who did not suffer such complications However, there was no significant difference in the mean diastolic blood pressure between the two groups [11]

Renal and renovascular disease Eleven patients (8 4 per cent) had parenchymatous renal disease Four had pyelographic evidence of chronic pyelonephritis (caliceal clubbing with thinning of the overlying renal cortex) Two patients had unilateral hydronephrosis, one associated with renal stone while a stone without evidence of obstruction was found in another There was one case each of medullary sponge kidney, bilateral polycystic kidneys and renal carcinoma (confirmed at surgery) Another patient had hypertension and persistent proteinuria following a septic abortion complicated by acute renal failure seven years previously

Six patients had bacteriological evidence of urinary tract infection but normal pyelograms

Ten patients (7 4 per cent) had pyelographic evidence of renal artery stenosis This was confirmed by arteriography, operation or autopsy in all except one In the latter case arteriography was unsuccessful but pyelography and an isotope renogram also suggested the diagnosis In no patient was there evidence to suggest whether the renovascular or adrenal lesion was first to develop

Further details of the renal and renovascular lesions appear elsewhere [11]

Biochemical abnormalities

Plasma aldosterone Mean plasma aldosterone concentration before treatment ranged from 10 4 to 192 5 ng /100 ml although plasma aldosterone was above normal at least once in all cases Plasma aldosterone was measured on two or more occasions in 54 patients, levels were persistently raised in 22 but only intermittently raised in 32 (see Table II)

Values were significantly higher among those patients in whom an adrenocortical adenoma was found at operation compared with those in whom a tumor was not identified (Fig 1)

Plasma sodium and total exchangeable sodium Mean plasma sodium concentration before treatment ranged from 135 7 to 150 5 mEq /L Mean values were significantly higher in the group of patients with a proved adenoma compared with those in whom a tumor was not found (Fig 1)

Total exchangeable sodium was measured

each patient was further subdivided according to the presence or absence of nodules in the attached and/or contralateral gland (Table III)

Adrenal glands without tumor The lesions in this group were subdivided into a number of patterns, according to the presence or absence of adrenal nodules and hyperplasia of the zona glomerulosa The weight of surgically removed glands was recorded in 19 cases twelve weighed less than 6 Gm and six were less than 4 Gm (upper limit of normal 6 Gm) In one patient parts of the adrenal cortex were normal histologically while others showed areas of hyperplasia of the zona glomerulosa with micronodules This variation may account for the apparently normal appearance of the zona glomerulosa in one patient (Table III) as only biopsies of these glands were taken at surgery [2]

Uncertain pathology In this series we encountered three examples of single unilateral lesions 0 25 to 0 5 cm diameter which defied light microscopic classification as adenoma or macronodule Each consisted of clear zona fasciculata type cells only with hyperchromatic nuclei and minimal or absent nuclear and cellular pleomorphism These lesions had features of either a tumor composed of uniform large hybrid cells or of a macronodule with zona fasciculata type cells (see Discussion)

Discussion

Age and sex This series again confirms that aldosterone producing adenomas are commoner among females [2, 6] However no clear sex difference was apparent among the smaller group in whom a tumor was not found [2] In our experience patients with an adenocortical adenoma are generally younger than those without an identifiable tumor [2] although others have not found this There was no significant difference between the groups in mean blood pressure before treatment [2]

Vascular complications It has been suggested that patients with essential hypertension and low plasma renin have fewer vascular complications than those with normal or high renin levels although this view has been widely challenged Some believe that primary hyperaldosteronism is a comparatively mild form of hypertension and it has been suggested[11] that this may be related to low circulating renin levels

In this series the high incidence of vascular complications is in striking contrast to the good prognosis in low renin essential hypertension reported by Brunner and colleagues [76] In addition there was histological evidence of malignant phase hypertension in four patients and other such cases have been described [84, 85] We find no evidence to support the view that primary hyperaldosteronism is a benign form of hypertension

Renal and renovascular lesions A few reports suggest that chronic secondary hyperaldosteronism may sometimes lead to the development of autonomous aldosterone excess which persists when the original stimulus has been removed [8] Secondary hyperaldosteronism may persist in salt losing nephritis when the sodium depletion has been corrected [90] Secondary hyperaldosteronism associated with malignant phase hypertension may occasionally persist when the blood pressure has been controlled and plasma renin levels return to normal [8] Autonomy in response to prolonged stimulation has been reported in other endocrine disorders Long standing hypocalcemia may lead to tertiary hyperparathyroidism in patients with malabsorption or renal disease [91, 92] while adrenal adenomas have been reported in Cushing's syndrome associated with a pituitary tumor [93] One possible example of tertiary hyperaldosteronism has been described This patient with renal disease and a documented high plasma renin value on one occasion later developed aldosterone excess associated with low plasma renin[94] at operation hyperplasia of the zona glomerulosa but no adenoma was found

The incidence of renal and renovascular disease in this series seems in general similar to that of large series from general hypertension clinics [7] If primary hyperaldosteronism commonly resulted from prolonged adrenal stimulation secondary to renal or renovascular disease one might expect a higher incidence of such abnormalities than in the general hypertensive population Because renal investigations and diagnostic criteria may vary between centers and because of possible selection bias we cannot exclude the possibility that renal disease may occasionally result in tertiary hyperaldosteronism however it seems unlikely that this mechanism is common It also seems unlikely that patients with adrenal hyperplasia represent an early stage in the pathogenesis of adrenal adenomas as in this series those with adenomas were significantly younger than those in whom a tumor was not found at operation

Table III Classification of the adrenal changes in 65 patients of this series

Groups	Histological subdivisions	Nos
1 Adrenocortical tumor*	Adrenal adenoma with hyperplasia of zona glomerulosa	20
	Adrenal adenoma with hyperplasia of zona glomerulosa and with nodules	25
2 No adrenocortical tumor	Hyperplasia of zona glomerulosa	3
	Hyperplasia of zona glomerulosa with micronodules	4
	Hyperplasia of zona glomerulosa with micronodules and macronodules	8
	Normal zona glomerulosa with micronodules	2
3 Uncertain pathology	*Either* an adrenal adenoma *or* a macronodule hyperplasia of zona glomerulosa with micronodules also present	3

An adrenocortical adenoma was reported in a further 17 patients in this series but tissue was not available for review

When patients with raised DOC values were compared with those with normal concentrations there was no significant difference in mean ages, there were seven and six females in the respective groups There was no significant difference between the groups in mean plasma concentrations of aldosterone sodium potassium total CO_2, urea renin or angiotensin II or in total exchangeable sodium potassium or total body water Mean blood pressure before treatment was similar as was the blood pressure response to treatment with spironolactone and following appropriate adrenal surgery

Plasma 18 hydroxy 11 deoxycorticosterone (18 OH DOC) Plasma 18 OH DOC was measured in 15 patients (20 estimations) Mean values ranged from 7 5 to 164 ng /100 ml (normal 10 to 50 ng /100 ml) A sub normal value was observed in two patients while in 5 others the value was variably raised (Fig 2)

Plasma corticosterone Plasma corticosterone was measured in 20 patients (25 estimations) Values ranged from 0 02 to 0 86 μg per 100 ml (normal 0 08 to 0 8 μg/100 ml) Values were marginally raised in two patients while a sub normal value was observed in another (Fig 2)

Correlations of total exchangeable sodium Total exchangeable sodium was measured before treatment in 32 patients in the proved adenoma group and in nine in whom a tumor was not found at operation Although the correlations reported here did not reach conventional levels of significance in the adenoma group there was a positive correlation between total exchangeable sodium and both systolic ($r \approx 0\ 22$) and diastolic ($r = 0\ 24$) blood pressure and with plasma aldosterone ($r = 0\ 25$), while there was a negative correlation with plasma renin concentration ($r = -0\ 26$) Such correlations would be expected if the hypertension in patients with an aldosterone producing adenoma is due to aldosterone induced sodium retention However, in the non adenoma group these correlations did not hold and total exchangeable sodium correlated weakly but negatively with systolic ($r = -0\ 08$) and diastolic ($r = -0\ 18$) pressure and with plasma aldosterone ($r = -0\ 79$), while exchangeable sodium correlated positively with plasma renin concentration ($r = 0\ 35$)

Plasma renin concentration and age In patients with essential hypertension there is an inverse correlation between plasma renin concentration and age,[72] possibly the result of renal adaption to prolonged elevation of blood pressure [73]

A similar inverse correlation with age was observed among patients in the non adenoma group ($r = -0\ 614$, $p < 0\ 01$) but *not* among those in whom an adrenocortical adenoma was found ($r = 0\ 129$, N S)

Pathology

In this series patients were divided into three main groups, those in whom a unilateral adrenocortical adenoma was found, those in whom a tumor was not identified and a small group in whom the adrenal lesion proved difficult to classify [24, 39, 74, 75]

Adrenal tissue was obtained at operation in 79 cases and at autopsy in three In 65 patients tissue was available for review and classification according to defined criteria [24, 75] and the findings are summarized in Table III (see also Figs 3 and 4) An adrenocortical adenoma was described in a further 17 patients but tissue was not subsequently available for review

Adrenocortical adenoma The majority of tumors weighed less than 3 Gm and measured 2 cm or less in diameter The adenoma was located in the left gland in 63 per cent The pathology of

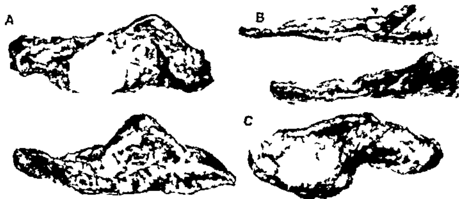


Fig 3 A B and C *A* An adrenal adenoma *1 cm in diameter* is contained wholly within the gland which also contains small nodules *B* The adrenal gland removed from another patient with hyperaldosteronism weighed 5 0 Gm and shows a thinned cortex and several small nodules the largest 0 5 cm in diameter *(arrow)* *C* The adrenal gland removed at surgery *contained a 1 0 by 0 25 by 0 5 cm yellow* intraglandular lesion Histologically it contained only clear lipid laden cells In monolayer culture aldosterone production was demonstrated Hence the tumor is functionally an adrenal adenoma Electron microscopic sections were not available for study

system[8, 2] Hyperaldosteronism in those patients in whom an adrenal tumor is not found might result from an unrecognized adrenal trophic stimulus[2] Nicholls and colleagues[9] recently described such trophic activity in a bioassay system using plasma from a single patient These workers speculated that prolonged stimulation might result in the development of adrenal autonomy (a form of tertiary hyperaldosteronism)

Another possibility is that the hyperaldosteronism in non adenoma patients results in an unknown way from prolonged hypertension perhaps with eventual adrenal autonomy Dobbie described capsular arteriopathy in most adrenal glands with nodular hyperplasia and speculated that this small vessel disease might initiate focal hyperplasia It is of interest that patients in this group show a significant inverse correlation between plasma renin concentration and age as is found in essential hypertension In contrast such a correlation was not found among patients with aldosterone producing adenomas

Pathology The characteristics of an aldosterone producing adenoma have been discussed[2, 18] Such tumors have a golden yellow cut surface and may project from the gland or be wholly intraglandular (Fig 3) With increasing size areas of necrosis hemorrhage and cystic change can occur On light microscopy such tumors may be composed of four cell types zona glomerulosa type cells zona reticularis type (compact) cell and large and small hybrid cells (cells with some features of glomerulosa cells and some of fasciculata cells) However few adenomas consist of one cell type only and all four types can occur in one tumor

Using non proliferating monolayer cultures it has recently been shown that zona glomerulosa type cells and both large and small hybrid cells can all produce aldosterone corticosterone and cortisol[12] However it is still not clear whether aldosterone producing tumors combine the functional features of both zona glomerulosa and zona fasciculata cells or consist functionally only of zona glomerulosa type cells Electron microscopic observations of both the large and small hybrid cells have indicated that they possess mitochondrial agranular endoplasmic reticulum and plasmalemmal features similar to those of zona glomerulosa and not of zona fasciculata cells[23, 1, 3, 14]

In the normal adult adrenal cortex the aldosterone producing zona glomerulosa has a focal distribution around its periphery[1] In primary hyperaldosteronism three different distributions of the zona glomerulosa may occur It may be *normal* exhibit focal hyperplasia (of increased width but with focal distribution) or diffuse hyperplasia (present around the entire periphery of the cortex and of normal or increased width) (Fig 4) When hyperplasia is marked areas of the zona glomerulosa may extend into the cortex in a tongue like *manner*

The adrenocortical nodules found in this condition have similar gross microscopic and ultra

Biochemical features Our results confirm and expand previous reports that the biochemical abnormalities in primary hyperaldosteronism are more severe among patients with an adrenocortical adenoma, compared with those in whom a tumor is not identified.[23,24,26,94] Mean plasma concentrations of aldosterone, sodium and tCO were significantly higher, and mean concentrations of potassium and renin were significantly lower. Total exchangeable sodium was also higher and total exchangeable potassium lower, in the adenoma group.

As previously reported,[95] hypokalemia occurred in all patients with an adrenocortical adenoma and was usually persistent. However, among 17 in whom an adrenal tumor was not identified, hypokalemia was less severe and usually intermittent, while three examples of normokalemic primary hyperaldosteronism were found in this group.

Hypokalemia occurred in 89 per cent of patients in this series. However this does not indicate the true incidence of hypokalemia in primary hyperaldosteronism, as many patients were initially referred because of unexplained hypokalemia. Furthermore the incidence will, to an extent, be influenced by the number of potassium measurements made, and in some instances the diagnosis may be first suspected when diuretic induced hypokalemia occurs.[6,17] Conn[16,96] has suggested that normokalemic primary hyperaldosteronism may be quite common in the hypertension population, but others have failed to confirm this.[97,101]

Although plasma aldosterone was elevated at least once in all cases, this abnormality was often intermittent.[102] For this reason, measurements of potassium seem as sensitive as single measurements of plasma aldosterone in screening for this condition, and are certainly more sensitive than single measurements of plasma renin concentration (Table II). This seems particularly so among patients with adrenocortical adenomas: hypokalemia was found in all and was persistent in 85 per cent, while plasma aldosterone was persistently raised in 71 per cent and renin was consistently suppressed in only 21 per cent.

Other corticosteroids Increased plasma levels of deoxycorticosterone (DOC) and corticosterone are not surprising, for these steroids are precursors of aldosterone[103] and their content is increased in adenomas associated with primary hyperaldosteronism.[104,104] Plasma deoxycorticosterone was raised in 50 per cent of patients and this added abnormality was seen in both the adenoma and non adenoma groups. Biglieri and colleagues[41] reported that DOC secretion rates were raised in four of 14 patients with an aldosterone producing adenoma. Crane and Harris[107] reported increased DOC secretion in a patient with primary hyperaldosteronism associated with an adrenal carcinoma, while DOC secretion was normal in each of two with an aldosterone producing adenoma.

It seems unlikely that the raised values of DOC we report could result from ACTH stimulation by stress, as in most cases concurrent plasma cortisol levels were normal. Aldosterone is a much more potent mineralocorticoid than is DOC,[108] so it is not surprising that raised levels of DOC, in addition to aldosterone, did not further exacerbate the biochemical abnormalities.

Plasma corticosterone was marginally elevated in two of 20 patients. Plasma corticosterone (measured by a double isotope derivative technique[61]) was raised in one of 12 patients with primary hyperaldosteronism previously reported by Brown and associates in 1968,[17] while Biglieri and colleagues[41] found a raised corticosterone secretion rate in seven of 17 patients with an aldosterone producing adenoma.

Adenoma and non adenoma cases The positive correlations between total exchangeable sodium and both systolic and diastolic blood pressure supports the concept that hypertension in patients with aldosterone producing adenomas is caused by sodium retention.[109] Because these correlations did not reach conventional levels of significance, conclusions must be tentative. However, such correlations were not seen in the non adenoma group, suggesting another cause for the hypertension in these patients.

Aldosterone producing adenomas were commoner in females, but such a sex difference was not observed in the non adenoma group. Patients with adenoma were also significantly younger. The fact that adenoma and non adenoma patients may be separated by statistical techniques such as quadric analysis[24] also suggests that these groups are different entities, rather than grades of the same disease.[110]

The combination of aldosterone excess and low plasma renin concentration is to be expected in any condition in which aldosterone secretion is stimulated other than by the renin-angiotensin

normal zona reticularis may be present There is arteriopathy of the capsular adrenal vessels of all nodule bearing glands

In vitro micronodules can form cortisol but not aldosterone while aldosterone can be extracted from adenomas but not from nodules [106, 111] Electron microscopy has shown that the cells of nodules lack the structural characteristics of aldosterone forming cells [113] Thus it seems that adrenocortical nodules may be an incidental finding in these patients and certainly are not an invariable feature (Table III)

Few pathological details have been reported by other workers of patients with primary hyperaldosteronism in whom a tumor was not found at operation However the material reported by Wolff and colleagues[1] has been reviewed by one of us (A M N) and changes similar to those found in the present series were seen hyperplasia of the zona glomerulosa with micronodules being the most frequent finding

While multiple tumors have been reported in some series previous studies have not appreciated the possibility that a tumor together with macro and/or micronodules can occur in the same and/or opposite glands This combination which was seen on several occasions in this present group might account for some of the reported examples of multiple or bilateral tumors

Although not encountered in this series hyperaldosteronism occurs rarely in association with adrenal carcinoma The pathological features have been reviewed recently [75, 77] The different cellular patterns found in benign tumors also occur in carcinomas Characteristically the cells are arranged in alveoli separated by prominent thick walled vascular sinusoids Pleomorphism mitotic activity necrosis and hemorrhage may or may not be present

Summary

The clinical and biochemical findings in 136 patients with low renin (primary) hyperaldosteronism are described A pathological diagnosis was made in 82 cases and a unilateral adrenocortical adenoma was found in 62 However a tumor was not identified in 17 the adrenal glands then usually showing hyperplasia of the zona glomerulosa often with nodular changes The adrenal lesion in a further three cases proved difficult to classify

Patients with an adrenocortical adenoma were significantly younger than those in whom a tumor was not found The female/male ratio was greater than 2 1 in the adenoma group, but no sex difference was observed in the group without tumor Vascular complications of hypertension occurred in 23 per cent and there was histologic evidence of malignant phase hypertension in four It is concluded that this condition is not a benign form of hypertension

Biochemical abnormalities were more marked among patients with an adrenocortical adenoma compared with those in whom a tumor was not found Mean plasma concentrations of aldosterone sodium and tCO_2 and mean exchangeable sodium were significantly higher while plasma potassium and renin concentrations and mean exchangeable potassium were significantly lower Although plasma aldosterone was above normal at least once in all levels were often only intermittently raised Hypokalemia occurred in all patients with a proved adenoma and was usually *persistent* Among patients in whom a tumor was not found hypokalemia was less severe and usually intermittent, while plasma potassium was persistently normal in three of 17 patients in this group

In addition to the aldosterone excess plasma deoxycorticosterone was raised in 13 of 26 patients plasma corticosterone was marginally raised in two and plasma 18 OH DOC in four of 15 There was a significant inverse correlation between plasma renin concentration and age in the non adenoma group but not among patients with an aldosterone producing adenoma Weak positive correlations were observed in the adenoma group between total exchangeable sodium and both systolic and diastolic blood pressure and between exchangeable sodium and plasma aldosterone concentrations Such correlations were not seen in the non tumor group The hypertension may have a different basis in these two groups

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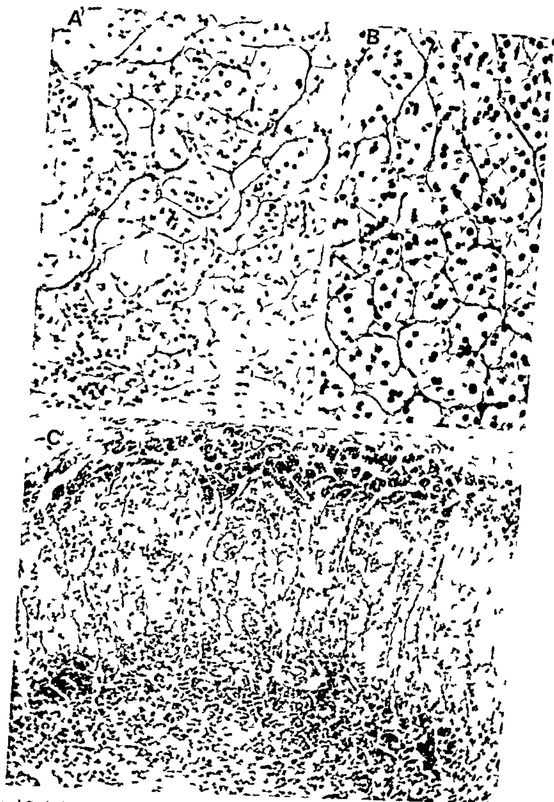


Fig 4 A B and C A An adrenocortical adenoma is shown consisting of large and small "hybrid cells The cells form cords and acini nuclear pleomorphism is present but not marked (Hematoxylin and eosin original magnification × 160) B Clear zona fasciculata like cells with small hyperchromatic regular nuclei comprise the nodule The cells are grouped in cords and acini and are separated by fibrovascular trabeculae (Hematoxylin and eosin original magnification × 300) C A hyperplastic zona glomerulosa with tongues extending into the cortex is shown together with the associated prominent vascular spaces The remainder of the cortex appears normal (Hematoxylin and eosin original magnification × 120)

structural features to those seen in Cushing s Syndrome and the so called non functioning nodule often found at autopsy [73] Nodules visible to the naked eye are called macronodules while those seen only microscopically are termed micronodules [71 73] All are composed of clear lipid laden cells with light and electron microscopic features similar to the clear cells of the normal zona fasciculata However, occasional nests of compact cells similar to those of the

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The hypertension complex

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Attention has been recently focused on hypertension because it is one of the most important underlying causes of vascular disease in the world and therefore a basic element in the process of aging and in death rate statistics Since much hypertension is presumably remediable or at least controllable we are often told that in order to prolong life there is public need to identify hypertension and treat it

This simplistic approach ignores the complexities of the hypertensive process possibly with some justification but anyone working with hypertensive patients will certainly agree that an understanding of the underlying mechanisms and their development is of inestimable help in determining appropriate therapy for the individual patient

Let us first consider the hereditary factor There are several types of genetic abnormalities that result in hypertensive diseases Pheochromocytoma is often hereditary and may be transmitted as an autosomal dominant trait There are types of pheochromocytoma that occur in association with thyroid carcinoma hyperparathyroid disease and neurofibromatosis and submucous nodules which are very often hereditary and may be found in both adrenal glands or may even be multifocal There is at least one type of hereditary chronic glomerulonephritis which is also probably transmitted as an autosomal dominant[2] and may be associated with hypertension Polycystic kidneys often have an hereditary substrate and can cause hypertension as well as renal failure

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We must now consider the vast pool of hypertension labeled essential' Many of these cases occur in families and most of us believe they have an hereditary substrate The blood pressures aggregate in families even in childhood[3] Stress hypertension is often lumped with essential hypertension and may be superimposed upon it Stress hypertension which is largely environmentally produced however may exist alone or may even subside entirely[4] It is not clear first whether essential hypertension is or is not fundamentally hereditary or merely familial whether a genetic defect if present is in the central nervous system sympathetic nervous system blood vessels tissues electrolytes endocrine glands or kidneys and most of the evidence suggests that it is multi rather than uni genic

The most important type of developmental or congenital hypertension is exemplified by coarctation of the aorta although it is conceivable that certain kinds of renovascular hypertension such as fibromuscular dysplasia may originate in this way

What can we learn from acute hypertension that may help us in an understanding of the subacute and more chronic types? Let us first consider acute glomerulonephritis Here salt and water is retained blood volume is increased Cardiac output is increased and edema may be present but is often minimal Plasma renin activity (PRA) is usually low or normal but may go up if fluids and sodium chloride are withheld Sympathetic discharge if anything should be decreased because of the baroreceptor effects unless the sodium and water in the baroreceptor regions have blunted these reflexes Not withholding sodium and water from the diet may result in increased hypertension with left ventricular failure and pulmonary edema even at levels of blood pressure that are only moderately

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The hypertension complex

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Attention has been recently focused on hyperten sion because it is one of the most important underlying causes of vascular disease in the world and therefore a basic element in the process of aging and in death rate statistics Since much hypertension is presumably remediable or at least controllable we are often told that in order to prolong life there is public need to identify hyper *tension* and treat it

This simplistic approach ignores the complexi ties of the hypertensive process possibly with some justification but anyone working with hypertensive patients will certainly agree that an understanding of the underlying mechanisms and their development is of inestimable help in deter mining appropriate therapy for the individual patient

Let us first consider the hereditary factor There are several types of genetic abnormalities that result in hypertensive diseases Pheochromo cytoma is often hereditary and may be trans mitted as an autosomal dominant trait [1] There are types of pheochromocytoma that occur in association with thyroid carcinoma hyperpara thyroid disease and neurofibromatosis and submucous nodules which are very often heredi tary and may be found in both adrenal glands or may even be multifocal There is at least one type of hereditary chronic glomerulonephritis which is also probably transmitted as an autosomal domi nant [2] and may be associated with hypertension Polycystic kidneys often have an hereditary substrate and can cause hypertension as well as renal failure

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We must now consider the vast pool of hyper tension labeled essential Many of these cases occur in families and most of us believe they have an hereditary substrate The blood pressures aggregate in families even in childhood [3] Stress hypertension is often lumped with essential hypertension and may be superimposed upon it Stress hypertension which is largely environmen tally produced however may exist alone or may even subside entirely [4] It is not clear first whether essential hypertension is or is not fundamentally hereditary or merely familial whether a genetic defect if present is in the central nervous system sympathetic nervous system blood vessels tissues electrolytes endocrine glands or kidneys and most of the evidence suggests that it is multi rather than uni genic

The most important type of developmental or congenital hypertension is exemplified by coarc tation of the aorta although it is conceivable that certain kinds of renovascular hypertension such as fibromuscular dysplasia may originate in this way

What can we learn from acute hypertension that may help us in an understanding of the subacute and more chronic types? Let us first consider acute glomerulonephritis Here salt and water is retained blood volume is increased Cardiac output is increased and edema may be present but is often minimal Plasma renin activity (PRA) is usually low or normal but may go up if fluids and sodium chloride are withheld Sympathetic discharge if anything should be decreased because of the baroreceptor effects unless the sodium and water in the baroreceptor regions have blunted these reflexes Not with holding sodium and water from the diet may result in increased hypertension with left ventric ular failure and pulmonary edema even at levels of blood pressure that are only moderately

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many normotensive subjects have blood pressures which rise or fall in response to environmental stimuli The degree of lability however can be roughly measured and is related more to the secretion of and response to epinephrine rather than nonepinephrine Increased lability may or may not be the harbinger of more fixed essential hypertension It can exist by itself in the young and into middle age and it may even be transient What is more essential hypertension and certainly renal hypertension may be relatively fixed with little lability even from the beginning Essential hypertension itself however tends to be more labile at its onset and to then become relatively more stable although higher especially when the kidneys become involved as manifested by nephrosclerosis [1] Labile hypertension may also have its onset in the more elderly patient and may be associated with the effect of arteriosclerosis on the baroreceptors [11] The systolic hypertension in the elderly caused by relative rigidity of the aorta and large blood vessels is also well known and this and the decreased sensitivity of the baroreceptors may exist together In the elderly one must also consider the possibility of renal artery stenosis due to atherosclerosis as a possible cause for the hypertension [6]

Although lability of blood pressure should be clearly distinguished from paroxysms of hypertension this is impractical A paroxysm of hypertension lasts for a few hours usually and then is followed by normal blood pressure for many hours and even for days It can be highly suggestive of pheochromocytoma but can occur as a stress phenomenon alone Also some pheochromocytomata can be associated with labile and even fixed hypertension or sometimes with normal blood pressure and therefore should be tested for widely since it is usually surgically curable Untreated a pheochromocytoma can subject the patient to high mortality risk if general anesthesia is required for incidental surgery or delivery of a baby [6]

Chronic hypertension has most often progressed in the course of the onset and development of essential hypertension but may involve other mechanisms as well It can occur for example because of sodium retention in primary aldosteronoma of the adrenal cortex It can also occur as part of Cushing s syndrome due it is believed to increased responsiveness to catecholamines [9] and also because of increased renin substrate and hence increased elaboration of angiotensin II [9] Chronic hypertension can also be caused by hyperreninemia either because of severe nephrosclerosis major renal arterial stenosis or juxtaglomerular cell tumor [21] The major renal artery stenosis in turn may be caused by atheromatosis fibromuscular dysplasia or renal artery aneurysm and occasionally by tumor compression as by a pheochromocytoma or a malignant tumor of various origin Chronic hypertension can also be caused by chronic renal disease such as glomerulonephritis pyelonephritis polycystic kidneys amyloidosis lupus nephritis etc Another cause of chronic hypertension especially in the upper part of the body is coarctation of the aorta To keep things in perspective however it should be mentioned that the bulk of chronic hypertensives fall into the essential category

The onset of chronic essential hypertension is probably in one way or another related to the catecholamines It is characterized by increased response to and secretion of epinephrine if there is a labile factor and an increased response to *norepinephrine* as a constant and persistent feature [13] If the hypertension is of renal origin however no matter how chronic or severe the increased response to norepinephrine may be absent in more than 50 per cent of the cases [3] The presence of increased norepinephrine reactivity in such cases therefore suggests underlying essential hypertension predisposing to the renal disease or coincidental in many cases because of the tremendous prevalence of essential hypertension

As has been already pointed out however the way in which the catecholamines are involved is still quite obscure It is known for example that in both normotensive and hypertensive subjects catecholamine release increases with age probably because of progressive stiffness of the walls of the baroreceptors with decreased sensitivity despite increased threshold and hence less inhibition of firing through the adrenergic sympathetic nerve complexes We also know that more released catecholamines reach vascular and cardiac receptors and less return to the neural network in essential hypertension than in normotensive subjects [3] but we do not know how much of this is attributable to simple hypertrophy of the blood vessel walls and how much is part of a basic chemical defect The role of epinephrine is

increased The left ventricle is not adapted to the increased load of increased cardiac output and either increased or inappropriately normal peripheral resistance The left ventricle therefore fails It is obvious here that salt and water retention up to a point can produce hypertension and this is true of other hypertensive states as well If one feeds excess salt and water to a normal person or animal, hypertension is prevented only because of the kidneys' ability to excrete the excess Even so, in some animals, moderate hypertension can be produced by feeding excess salt and water for a long period [5]

When glomerulonephritis becomes sub acute, however, and we are faced with the nephrotic syndrome several things happen to reduce the blood pressure, often to normal levels despite high PRA First, the low plasma proteins and anemia reduce blood viscosity although the anemia increases cardiac output Second the excess sodium and water is now in the extracellular spaces and the sodium is not concentrated near the blood vessels where it can produce vasocon striction by a variety of effects Some of these effects are blood vessel wall edema[6] and inhibition of re uptake of catecholamines [7] The blood vessel receptors may become refractory to circulating angiotensin II as well as to norepinephrine, both of which may leak into the intercellular fluid It is interesting that high plasma renin activity is also found in cirrhosis of the liver with ascites, despite normal blood pressure probably due to the same mechanisms In the syndrome reported by Bartter and associates[8] (high PRA, juxtaglomer ular cell hypertrophy high aldosterone normal blood pressure, low serum potassium and normal sodium), the difficulty seems to be an excess of prostaglandin A or E since indomethacin can reverse the process

There is another type of acute hypertension which is produced by increased vasoconstriction with or without increased cardiac output This occurs for example, in a clinical situation in which there is an acute increase in intracerebral pressure as in acute subdural hematoma acute urinary tract obstruction, or iatrogenically, if one infuses angiotensin or arterenol or in so called stress hypertension occasioned by acute anxiety or during a paroxysm of hypertension in a patient with pheochromocytoma or in an animal in which one has produced renovascular obstruction acute ly The cause of such hypertension is usually the release into the blood stream or the release locally from autonomic nerve endings of such vasoactive substances as epinephrine, norepinephrine and angiotensin II and perhaps others not yet clearly identified These substances stimulate vascular and cardiac receptors which in turn affect the adenylcyclase, 3, 5, AMP or 3 5, GMP, and phosphorylase systems,[9] producing increased smooth and cardiac muscle contraction, as a rule or in the case of epinephrine, increased heart rate and cardiac output at certain dose levels and increased vasoconstriction at higher levels [10] These are not simple reactions but are rather complex interactions, the increased pressure, for example, tending to be modified by an opposite effect via the baroreceptors [11] The prostaglandins are also modifying substances,[12] and various other hormones may be involved temporarily If the reaction is severe myocardial blood vessels and the heart itself may be affected and acute ventric ular failure may be the result of such a process as well, because of the acutely increased load on the left ventricle unprepared by previous hypertro phy Again, blood pressure levels as low as 180/100 or higher ones may produce this effect in the damaged but not hypertrophied heart

In chronic hypertension whether essential or renal, the mechanisms are considerably more complex and therefore less well explored and understood The first question to ask is how is the hypertension initiated, and the answer is often an indication merely of the prejudices of the one answering My answer will also involve prejudice as well as prolonged observation and some exper imental data

Hypertension is extremely difficult to evaluate in childhood First of all the blood pressure normally is lower as one descends the scale of years into childhood and infancy Secondly the stress of blood pressure taking itself is greater in the child than in the adult and particularly in the infant Fluctuations are therefore greater and trends are difficult to evaluate It is of interest that blood pressure levels tend to aggregate in families and to be high in so called hypertensive families There is little doubt however, that most essential hypertension is of genetic origin and that the defect must therefore be present from birth but can only be made manifest by environ mental stimulation [13]

It might be pertinent now to discuss lability of blood pressure All hypertensive patients and

substances including angiotensin II tend to leak into the fluid sumps and not reach vascular receptors Also blood viscosity decreases because of anemia and hypoproteinemia although cardiac output may increase

2 What about congestive heart failure? *Possible answer* There is increased peripheral resistance but the cardiac output is usually decreased and therefore blood pressure may remain normal If there is edema many of the mechanisms cited in paragraph 1 above may obtain

3 Why is there often little hypertension in polycythemia vera where viscosity can often be doubled? *Possible answer* The cardiac output remains normal or low most of the blood being in venules and veins Are the arterioles dilated or constricted? What is the effect of the increased available oxygen?

4 Why is the kidney so vulnerable in hypertension? *Possible answer* The glomeruli are the only capillaries between two arterioles and one of the kidneys chief functions is the regulation of fluid and electrolyte balance The response of the kidneys to hypertension are therefore out of phase with the rest of the body in the direction of greater vasoconstriction

5 Why is the brain so vulnerable? *Possible answer* Sympathetic responses of blood vessels of the cerebral tissue itself are relatively weak in comparison to skin muscle intestine or kidney These cerebral vessels are therefore more likely to develop microaneurysms that lead to hemorrhage and edema as the blood pressure rises The increased spinal fluid pressure on the other hand is an accelerating factor since it stimulates the vasomotor centers The retina reflects events in the brain

6 What is the role of the renal vasodilator substances such as prostaglandins [7] kinins [31] antirenins and others? *Possible answer* A deficiency of these substances may contribute to essential hypertension but much more research is needed to delineate their exact role The case of Bartter s syndrome suppressed by the prostaglandin inhibitor indomethacin is very provocative although the exact cause of the syndrome is still obscure

7 What is the relationship of atherosclerosis to hypertension? *Possible answer* This is a complex question indeed What is known *is that* hypertension is one of the factors that accelerates atherosclerosis although the latter may exist without hypertension Also atherosclerosis may increase hypertension in several ways It can for example because of decreased elasticity increase systolic and decrease diastolic pressure It can decrease the sensitivity of the baroreceptors and it can produce unilateral or bilateral renal artery stenosis In the latter instances surgery is indicated especially if the PRA is increased in the affected renal vein or if the kidneys are very compromised and there are no other atherosclerotic risks Also a trial of antihypertensive medical therapy is usually warranted in such cases The situation is different in the younger patient especially with fibromuscular renal artery dysplasia If the criteria delineated above are met the results of surgery are considerably better Surgery may involve bypass of the stenosis patch graft or rarely nephrectomy If there is pre existing essential hypertension or secondary nephrosclerosis of the opposite kidney the results of operation may only be moderate and antihypertensive drug therapy may still be required Because of predisposition and incidence the combination of essential hypertension with atherosclerotic renal artery stenosis may be as high as 40 to 50 per cent

Therapy

To subject patients to mass therapy for hypertension to achieve epidemiological results is in my opinion absurd and doomed eventually to failure In the first place there are patients who *should not* be treated at all and therefore medications can do them harm This would include *transient* stress hypertension some cases of early stress hypertension and some patients with remediable surgical conditions Also *no two patients* can be treated alike for many reasons including sensitivities stages of the disease associated conditions etc Therefore this business of step wise medication as prescribed in many journals and pharmaceutical company releases should be scrapped In addition the therapy for hypertension is continually changing *as new data* and new drugs emerge Each physician must be educated in all this and use his trained judgment in prescribing therapy Nurse practitioners and aides can be trained in the same way by knowledgeable physicians if the load becomes too great

As to specific drugs there is no law that states that every patient should be started *with reserpine or* with a diuretic Reserpine itself is almost

not at all clear and it is not known whether epinephrine hyperreactivity can evolve into norepinephrine hyperreactivity or whether these are two separate processes which may exist together or separately There is now evidence from dose-response curves that hyperreactivity to norepinephrine consists not only of the effect of smooth muscle hypertrophy but also of an intrinsic hypersensitivity to the neural hormones, but we do not know the significance of this[2]

Let us now consider so called secondary factors which it must be admitted, may come to dominate the hypertension in various stages of the disease Some of these have been studied extensively and some are relatively poorly understood Let us first consider electrolyte and fluid balance together with the renin-angiotensin-aldosterone systems[23 24] The organism has developd many safeguards to insure proper fluid and electrolyte homeostasis If the blood pressure begins to rise for any reason these mechanisms come into play The state of sodium and water equilibrium is generally reciprocal to the renin-angiotensin system and its cascades If the initial increase in blood pressure causes increase in glomerular filtration and loss of electrolytes and water, particularly sodium the renin-angiotensin system will come into play to retain these substances There is also a balance between the renin-angiotensin system which stimulates aldosterone to retain sodium and aldosterone itself or its effects on the electrolytes which tend in turn, then, to inhibit the renin-angiotensin system There is therefore always a balance between the two systems which may be tipped in either direction producing hyperreninemia and severe hypertension on the one hand or pseudohyperaldosteronism with sodium and fluid retention, potassium loss, and hypertension on the other Aldosteronoma or a tumor of the juxtaglomerular apparatus is probably autonomous and not at all, or less, influenced by the factors discussed above Their effects and end results, however, are similar In both the latter instances surgery is usually necessary whereas this is not the case when the conditions are not autonomous

There are other endocrine conditions including tumors that are related to hypertension and their mechanisms often differ In Cushing's syndrome for example, the glucocorticosteroids produce an increase in renin substrate[9] as well as in vascular reactivity[19] to vasoactive substances thus producing hypertension In hyperparathyroidism, hypertension may be produced by the effect of increased available calcium on the kidney and vascular smooth muscle[3] In hyperthyroidism the increased cardiac output may be associated with mild hypertension[26] but in myxedema, hypertension may be caused by increased production of and sensitivity to catecholamines[27] The reason for the high incidence of hypertension in diabetes mellitus and in gout as well as in acromegaly is not clearly understood Hypertension can also be seen in children with dysautonomia (Riley Day syndrome) as they grow older[28] In hyperviscosity syndromes, such as are seen sometimes in multiple myeloma etc and in polycythemia vera, the hypertension is usually mild and can be caused by increased blood viscosity,[29] whereas in Gaisboeck's syndrome the polycythemia is caused by decreased plasma volume which is in turn the result of the hypertensive condition itself[30] As the hypertensive disease develops structural changes begin to take place, particularly in the heart and arterioles, and especially so in chronic essential hypertension The left ventricle working against increased peripheral resistance, becomes hypertrophied and the septum bulges into the right ventricle This process is reversible unless fibrosis has intervened because of subendocardial ischemia or coronary artery stenosis Similarly the arteriolar muscle which must work harder to maintain the increased resistance so as not to flood the capillaries with fluid, also develops concentric hypertrophy with increasing layers of muscle and elastic tissue, all of which is reversible unless fibrosis intervenes, in which case the changes become less reversible Necroses such as are seen in malignant hypertension and aneurysms such as are found in periarteritis nodosa are of course, reversible only by the production of extensive scarring Intimal hypertrophy, thrombosis, and recanalization are integral effects of malignant hypertension and all these changes are accelerating factors in the disease

Here are presented possible answers to several unanswered questions with respect to mechanisms

1 Why is there often no hypertension in cirrhosis of the liver with ascites and edema and in other edematous states such as nephrotic syndrome where plasma renin activity can be very high? *Possible answer* The vasoactive

substances including angiotensin II tend to leak into the fluid sumps and not reach vascular receptors Also blood viscosity decreases because of anemia and hypoproteinemia although cardiac output may increase

2 What about congestive heart failure? *Possible answer* There is increased peripheral resistance but the cardiac output is usually decreased and therefore blood pressure may remain normal If there is edema many of the mechanisms cited in paragraph 1 above may obtain

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As to specific drugs there is no law that states that every patient should be started with reserpine or with a diuretic Reserpine itself is almost

not at all clear and it is not known whether epinephrine hyperreactivity can evolve into norepinephrine hyperreactivity or whether these are two separate processes which may exist together or separately There is now evidence from dose-response curves that hyperreactivity to norepinephrine consists not only of the effect of smooth muscle hypertrophy but also of an intrinsic hypersensitivity to the neural hormones, but we do not know the significance of this

Let us now consider so called secondary factors which it must be admitted may come to dominate the hypertension in various stages of the disease Some of these have been studied extensively and some are relatively poorly understood Let us first consider electrolyte and fluid balance together with the renin-angiotensin-aldosterone systems [3, 4] The organism has developd many safeguards to insure proper fluid and electrolyte homeostasis If the blood pressure begins to rise for any reason these mechanisms come into play The state of sodium and water equilibrium is generally reciprocal to the renin-angiotensin system and its cascades If the initial increase in blood pressure causes increase in glomerular filtration and loss of electrolytes and water, particularly sodium the renin-angiotensin system will come into play to retain these substances There is also a balance between the renin-angiotensin system which stimulates aldosterone to retain sodium and aldosterone itself or its effects on the electrolytes which tend in turn then, to inhibit the renin-angiotensin system There is therefore always a balance between the two systems which may be tipped in either direction producing hyperreninemia and severe hypertension on the one hand or pseudohyperaldosteronism with sodium and fluid retention potassium loss, and hypertension on the other Aldosteronoma or a tumor of the juxtaglomerular apparatus is probably autonomous and not at all or less influenced by the factors discussed above Their effects and end results however are similar In both the latter instances surgery is usually necessary, whereas this is not the case when the conditions are not autonomous

There are other endocrine conditions including tumors that are related to hypertension, and their mechanisms often differ In Cushing's syndrome, for example the glucocorticosteroids produce an increase in renin substrate [6] as well as in vascular reactivity [19] to vasoactive substances thus producing hypertension In hyperparathyroidism, hypertension may be produced by the effect of increased available calcium on the kidney and vascular smooth muscle [5] In hyperthyroidism the increased cardiac output may be associated with mild hypertension [6] but in myxedema, hypertension may be caused by increased production of and sensitivity to catecholamines [7] The reason for the high incidence of hypertension in diabetes mellitus and in gout as well as in acromegaly is not clearly understood Hypertension can also be seen in children with dysautonomia (Riley Day syndrome) as they grow older [28] In hyperviscosity syndromes such as are seen sometimes in multiple myeloma etc and in polycythemia vera, the hypertension is usually mild and can be caused by increased blood viscosity [29] whereas in Gaisboeck's syndrome the polycythemia is caused by decreased plasma volume which is in turn the result of the hypertensive condition itself [30] As the hypertensive disease develops, structural changes begin to take place particularly in the heart and arterioles, and especially so in chronic essential hypertension The left ventricle working against increased peripheral resistance becomes hypertrophied and the septum bulges into the right ventricle This process is reversible unless fibrosis has intervened because of subendocardial ischemia or coronary artery stenosis Similarly the arteriolar muscle which must work harder to maintain the increased resistance so as not to flood the capillaries with fluid also develops concentric hypertrophy with increasing layers of muscle and elastic tissue all of which is reversible unless fibrosis intervenes, in which case the changes become less reversible Necroses such as are seen in malignant hypertension and aneurysms such as are found in periarteritis nodosa are of course reversible only by the production of extensive scarring Intimal hypertrophy, thrombosis, and recanalization are integral effects of malignant hypertension and all these changes are accelerating factors in the disease

Here are presented possible answers to several unanswered questions with respect to mechanisms

1 Why is there often no hypertension in cirrhosis of the liver with ascites and edema and in other edematous states such as nephrotic syndrome where plasma renin activity can be very high? *Possible answer* The vasoactive

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an obsolete drug since it produces serious depression in some patients and bleeding peptic ulcers in others Other drugs are more efficient and less hazardous

As for diuretics, the major virtue of the thiazides is that they are effective, cheap and available in many forms They also however, accentuate diabetes produce gout and often cause gastrointestinal disturbances as well as skin rashes In addition, the potassium loss they produce often requires potassium supplementation and hence more pills Spironolactones on the other hand, though perhaps less effective, are very benign and produce few such side actions They may however, cause breast hypertrophy in the male and menstrual disturbances in the female Furosemide is another choice with almost though not quite the incidence of the side effects of the thiazides

Methyldopa is often recommended as a second or third drug It is not a very effective drug and requires constant vigilance against a positive Coombs test and possible hemolytic anemia It may also produce though rarely, severe hepatic damage It does produce lower plasma renin activity

One of the most effective drugs available is guanethidine I have no objection to using it in milder hypertension provided the dose is carefully monitored The postural hypotension frequently found the frequent bowel movements and ejaculation curtailment are its chief side effects but are not very troublesome Neither guanethidine nor methyldopa should be used without a diuretic in order to prevent the salt and water retention produced by the former drugs

One of the most frequently used first drugs today is propranolol It is good for the labile or adrenalin induced hypertensive patient and is very benign in the severe hypertensive, especially one with angina Heart failure and asthma are contraindications The drug may then be supplemented either by an alpha blocking drug like phenoxybenzamine, or by hydralazine or minoxidil or any one of the other direct acting drugs now marketed These include prazosin and may include other not yet marketed vasodilating drugs acting directly to inhibit vascular smooth muscle contraction The addition of a diuretic then produces normotension in most of these cases with little or no postural hypotension The drugs most frequently used today for hypertensive emergencies are diazoxide and sodium nitroprusside These drugs are usually used in a hospital setting, however

The most important thing to remember in treating hypertensive patients is to individualize according to history, stage of the disease, and underlying diagnosis Also, one must begin slowly and make increments or additions gradually in accordance with the pharmacology of the drugs and the individuality of the patient

Summary

The complex of factors that operate in the genesis as well as the development of various types of hypertensive disease is discussed Questions are asked and possible answers given to only a few of the unsolved problems of hypertension The treatment of hypertension especially with drugs, is then discussed in the light of these complex mechanisms

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Large collateral channels have also been observed in patients with ventricular hypertrophy,[16] anemia[1, 20] cor pulmonale[7] and emphysema[13, 7] Although the precise physicochemical factors determining this enlargement are unclear myocardial hypoxia would appear to be a common denominator

Thus human myocardial collateral channels have the capacity to enlarge However the chronicity of the above conditions associated with large caliber collaterals raises doubts about the possibility of enlargement as an acute adaptive mechanism Analyzing autopsy material Fulton[21] observed the number of large scale coronary anastomoses increased as the duration of angina pectoris increased He found that patients dying with a history of angina spanning less than three months had only a few large scale anastomoses and concluded that years were necessary for collateral enlargement to occur in man Using histologic and radiologic techniques Jones[7] examined hearts of patients dying after myocardial infarction and determined that collaterals were not well developed for eight weeks after the acute event This impression of depressingly slow collateral development however may not be correct The case report of a young boy who sustained traumatic perforation of the right atrium and ventricle is pertinent[23] During an uncomplicated operation the chambers were repaired Several days later a continuous murmur was heard and cardiac catheterization nine days after the initial injury revealed a fistula between the right coronary artery and right atrium Coronary angiography revealed retrograde opacification of the right coronary artery distal to the fistula via extensive intercoronary collaterals from the left anterior descending and circumflex arteries Other observations support this initial report Furthermore spasm of the right coronary artery around the catheter during injection of contrast medium in a patient with normal coronary arteries has produced opacification of numerous collateral vessels to the left circumflex artery There is thus some evidence that sizeable collaterals are either already present or can form within days a more promising prospect than the autopsy studies would have indicated

Functional effects Morphology however does not provide reliable estimates of function and the presence of collaterals that can enlarge acutely is not sufficient to prove their importance Porter[7] in 1901 wrote The passage of a fine injection mass from one vascular area to another proves nothing concerning the possibility of the one area receiving its blood supply from the other Thus a distinction between anatomic and functional end artery was being made However simple observations have suggested that coronary collaterals do play a functionally important role Numerous cases of total coronary obstruction without myocardial damage have been documented[6, 8, 3, 1, 21, 27] and Lesbre and colleagues[8] stated that 6 to 8 per cent of examined hearts with coronary occlusion had no evidence of tissue necrosis In Baroldi s material[29] as many as 44 per cent of patients with one or more coronary artery obstructions did not have histologic evidence of myocardial necrosis Carleton and Boyd[30] described the case of a young man with traumatic laceration of the left anterior descending coronary artery Prior to ligation of both ends vigorous back bleeding from the distal portion was observed Subsequent to ligation the patient developed no electrocardiographic evidence of infarction suggesting pre formed collateral vessels were able to metabolically support the area formerly perfused by the left anterior descending artery

Infarction size is frequently smaller than the perfusion area of the obstructed vessel[5, 1, 27, 31] Furthermore some patients develop myocardial necrosis in areas remote from those of a recently occluded vessel[8] In these latter cases it is postulated that the primary vessel to the infarcted area had been occluded sometime in the past with the myocardium being supplied by collaterals originating from the more recently occluded vessel These observations support the functional significance of coronary collaterals

Attempts to evaluate collateral channels in other than postmortem specimens have yielded conflicting results Matched populations with equally severe coronary occlusive disease and differing only in the presence or absence of collateral vessels have been studied Whereas some investigators have concluded collaterals have no effect on left ventricular performance[37, 38] regional ventricular contraction[1] ability to exercise or prognosis[33, 3] others have documented beneficial effects on left ventricular function and contraction patterns[47] as well as survival[8, 48] Perhaps these studies err in the definition of the study groups As stated by Schaper[49] and by

The functional value of coronary collaterals in myocardial ischemia and therapeutic approach to enhance collateral flow

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The collateral circulation, blood flowing in single or interconnecting systems of channels, is alternative to a major vascular conduit which has become non-functional Thus a collateral channel is an initially unused pathway which is recruited only after failure of the original vessel to permit normal flows Collateral vessels may be preformed, in which case there is immediate expansion and subsequent growth in response to the new stresses, or may be formed de novo where the potential for cellular transformation is preserved Following coronary obstruction, blood supply to jeopardized myocardium must be delivered by collateral channels Although alteration of myocardial metabolism may be important to the salvage of ischemic tissue development of an adequate collateral supply is central to ultimate tissue survival

Human studies

Anatomic demonstration The importance of the collateral circulation to myocardial function in man continues to be questioned and until recently documentation of the presence of collaterals in normal human myocardium was uncertain Although collaterals in the human heart were first described by Lower in 1671 the treatise by Cohnheim and von Schulthess Rechberg[1] in 1881 labeled coronary arteries 'end arteries' because of the inability to demonstrate anastomoses between the three major coronary systems of the normal heart These conclusions were refuted by Spalteholz[2] in 1907 who announced that connections between coronary arteries were indeed present Other prominent anatomists quickly agreed[3-5] However, in 1938 Schlesinger[6] described his technique for injecting coronary arteries with a colored lead agar mass producing radiographs and dissecting the vessels He and his co workers examined over 1,000 hearts in the ensuing 13 years,[7-9] and concluded that anastomoses existed in only 10 per cent of normal human hearts Subsequent careful radiologic investigations with radiopaque[10, 11] or bismuth oxychloride gelatin[12] lipoidal masses latex injection studies[13, 14] and vinylite casts[15] of the coronary tree all demonstrated numerous 200 μ anastomoses in practically 100 per cent of normal human hearts Rodriguez and Robbins[16] repeated some of Schlesinger's work and determined that technical factors prevented Schlesinger from identifying collaterals in normal hearts With minor modifications of the technique, they demonstrated collateral channels in all examined normal hearts Thus collateral channels do exist in normal human myocardium

Collateral enlargement Enlargement of collateral conduits in man is an accepted observation Anatomic-pathologic[6, 8 10 13] and coronary angiographic[17] studies of patients with coronary obstructive disease have frequently revealed tortuous collaterals with diameters in excess of 1 mm The presented data however do not indicate whether the enlargement occurs prophylactically or subsequent to a coronary occlusion These anastomoses can also enlarge without the stimulus of a coronary occlusion or constriction

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demonstrated a direct relationship between collateral channels and infarct size These investigators ligated the left anterior descending coronary artery in dogs and then touched the edges of distribution of the ligated vessel with a hot cautery The size of the infarct was always much larger than that in animals with an isolated coronary ligation The burns were small and caused no central infarction in control animals Hence epicardial collaterals in the dog do serve to limit the extent of ischemia

Eckstein s early work demonstrated a significant relationship between collateral development and electrocardiographic manifestations of ischemia Coronary ligation in pigs produced marked ischemic changes Retrograde coronary flow was negligible and no collaterals could be identified by postmortem coronary injection of barium sulfate mass On the other hand the electrocardiogram of dogs following abrupt coronary occlusion was much less abnormal Retrograde coronary flow was much higher in this species and generally those animals with the highest flows had minimal ischemic abnormalities Furthermore in one half of the canine hearts the barium suspension passed from one coronary system to the other via anastomotic channels Schley and co workers[74] have also demonstrated an inverse relationship between the magnitude of collateral development and the degree of ischemic electrocardiographic abnormalities following coronary occlusion More recently Stephan and colleagues monitored S T segment changes following coronary occlusion in the dog by doing epicardial mapping during right atrial pacing and before and after practolol infusion Collateral vessels were identified by postmortem injection For any given level of heart rate left ventricular dP/dt or myocardial oxygen consumption the magnitude of S T elevation was significantly less in the animals with more abundant collateral anastomoses

Survival after acute coronary occlusion has also been correlated with the degree of collateral development As noted previously the mortality rate in pigs is much higher than that in dogs[5, 5] Approximately two thirds of dogs survive for at least eight hours after acute coronary ligation[60] Those dying prematurely have significantly fewer collateral anastomoses than those living for at least eight hours[6] No dogs with poorly developed collaterals survived left circumflex occlusion whereas 96 3 per cent of animals with well developed collaterals survived the acute event Interestingly pigs will survive coronary occlusion if an initial 85 per cent stenosis is produced at least 12 days before occlusion[78] At the time of sacrifice these animals have rich anastomotic networks Garza and colleagues[7] have shown the electrical threshold for ventricular fibrillation in dogs following coronary ligation to be significantly higher in hearts with good collateral development

Effect on infarct size A quantitative relationship between collateral vessel development and the size of infarcts followong coronary obstruction has been derived There is a significant inverse relationship between the amount of blood flow to the ischemic myocardium following occlusion and the measured areas of the ultimate infarct at one to seven days after the initial event[7, 9] This relationship was established in dogs with either abrupt or gradual coronary ligations[8] In one study myocardial necrosis was observed only when endocardial blood flow was reduced by approximately 50 per cent[8] Below this level the inverse relationship between flow and infarct size was linear Thus pre formed collaterals have the capacity to limit both myocardial ischemia and necrosis However therapeutic measures intended to salvage jeopardized myocardium during the acute phase of infarction must rely on collateral recruitment and potential expansion

Following coronary stenosis and obstruction the development of a transanastomotic gradient results in collateral dilatation This dilatation is accompanied by rupture of the internal elastic membrane[3] An initial phase of rapid radial growth occurs where cellular material is used to produce further dilatation of seemingly maximally stretched vessels Within 3 to 4 days the luminal diameter of the collateral vessel in the dog may increase more than tenfold

Infarct size is quite different in groups of dogs with abrupt and gradual coronary occlusions Solid emboli into the left anterior descending coronary artery produce infarcts averaging 20 per cent of the left ventricular cross sectional area whereas hollow emboli which gradually thrombose over a five to ten hour period produce average infarct sizes of only 4 per cent with half of the animals having no grossly detectable areas of necrosis[1] The only apparent difference

Lavine and associates,[58] the degree of collateralization reflects the severity of the coronary obstructive disease. Therefore, patients with collateral networks may have had more intense ischemia to initiate their development, thus making comparison with patients without collaterals hazardous.

Collateral flow in man has been quantitated infrequently. Injection of radioisotopes into the exposed left ventricular myocardium[51] or into a saphenous vein bypass graft[5] or measurement of retrograde flow from a bypass graft attached to a proximally occluded coronary artery[53] can be done only at the time of left thoracotomy. Therefore, these measurements have limited value.

Thus studies in man have demonstrated the existence of a preformed collateral network in normal myocardium which has the capacity to enlarge and which appears to have a protective effect. However, the physiology of collateral development, the acute changes occurring in ischemic myocardium, the magnitude of their beneficial effect, and the extent to which they can be acutely affected by pharmacologic or mechanical interventions cannot easily be studied in human subjects. With experimental animals it has been possible to approach more closely the answer to the possible significance of the collateral circulation. Although results in the experimental animals cannot be directly applied to man, these experiments have helped us to better understand the role of the collateral vessel.

Animal studies

Anatomic demonstration. The two most commonly used animal models are the pig and dog. The pig has three major coronary arteries supplying the left ventricular myocardium, a situation analogous to that in man.[54] The dog, however, has a small right coronary artery which supplies only the right ventricular free wall.[55] Collateral anastomoses have the same histology in all three species.[4] Canine collaterals are generally epicardial in location,[4, 54, 5] although endocardial connections do exist.[11] Man has numerous anastomoses throughout the myocardial wall, especially near the epicardial and endocardial surfaces.[13, 4, 55, 56] The ratio of blood flow to the epicardial and endocardial halves of the left ventricular wall following coronary occlusion is similar in both primate and canine species. The pig, on the other hand, has only sparse endocardial and endomural connections.[11, 54, 5] This natural difference between dog and pig serves to illustrate the significance of a collateral circulation. Following abrupt[59] or even more gradual coronary occlusion in the pig, the mortality rate is near 100 per cent and survivors of gradual occlusion have large, transmural infarcts.[59] The dog survival rate, however, usually exceeds 67 per cent,[60] and only small areas of necrosis develop. The pig with its sparse collaterals is quite vulnerable to the adverse effects of deprivation of myocardial nutrition, whereas the numerous collateral channels in the dog protect the myocardium and the animal. Quantitation of collateral blood flow to ischemic areas confirms that pig collaterals deliver less than one fourth of the flow carried by canine channels.[61, 62]

Functional effects. Although visual demonstration of canine collateral anastomoses is not difficult, functional significance is not immediately apparent. Flow to acutely ischemic areas averages 10 to 30 per cent of normal levels,[6] and intravenous injections of either dye,[64] fluorescein,[65] or P^{32} erythrocytes[63] demonstrate obvious staining or radioactivity in the distal myocardial areas deprived of antegrade flow. Wiggers, however, believed that this blood flowing through the ischemic area must be too sluggish to serve a useful purpose. Paradoxical bulging of ischemic myocardium following coronary occlusion supports this conclusion.[8] However, these same ischemic areas can be observed to contract normally several weeks later, at a time when resting regional blood flow to areas distal to the occlusion has actually returned to the pre-occlusion level.[70, 71] Thus dog, like man, has collaterals which can enlarge and which are functional. But one must question whether these anastomotic vessels have any value immediately following coronary occlusion, and whether their development can be altered to provide additional protection to jeopardized myocardium.

As in man, canine coronary arteries can be occluded without production of necrosis,[7] while infarcts that do develop are smaller than the perfusion area of the ligated vessel.[7] Schaper and co-workers[3] have tried to quantitate this relationship and estimate that only one half of the perfusion area of the occluded left anterior descending coronary artery in dogs is infarcted. These results have recently been confirmed by Rivas and colleagues.[72] Bobb and associates

substantially higher[83 74 8 4 84-85] The epicardium is in effect a border zone Attempts to decrease infarct size may be attempts to convert transmural to endocardial infarcts

Potential therapeutic benefits

Removal of obstructions to antegrade flow more than 1½ hours later does not result in the expected restoration of normal blood flow to the ischemic region[92] This no reflow phenomenon has been attributed to local edema with resulting compression of microvasculature[93] Although most apparent when flow restoration is attempted cellular edema occurs in ischemic tissue as well Therefore therapy directed at reduction of cellular edema and hence collateral compression would appear to be a potentially successful means of limiting myocardial ischemia The hyperosmotic agent mannitol has been administered to dogs with acute and chronic myocardial ischemia with resulting increases in collateral and total coronary blood flows and myocardial contractility and decreases in the magnitude of epicardial S T segment elevation and extent of myocardial necrosis[95] Although partial reversal of no reflow is undoubtedly part of the drug s beneficial effect a direct action on vascular smooth muscle may also be involved because of mannitol s ability to enhance blood flow to normal myocardium

Another seemingly promising intervention would be increase of aortic diastolic pressure or coronary perfusion pressure Elevation of blood pressure in animals with acute coronary occlusion diminishes myocardial ischemia despite the theoretical adverse effects of increased afterload[97] Diastolic counterpulsation increases collateral blood flow[8] as well as the number of collaterals visualized by postmorten angiography In a recent study Watson and co workers[10] observed that the combination of mannitol and counterpulsation increased collateral flow to acutely ischemic regions of the left ventricle more than either intervention alone

Although vasodilators may decrease coronary arterial resistance and increase coronary blood flow few have the ability to augment coronary collateral flow Furthermore dilatation of the distal coronary arterioles may produce small decreases in coronary perfusion pressure which in turn may cause actual diminution of collateral supply (coronary steal [1]) The nitrates however have been shown to elicit primary dilatation of coronary collateral channels which persists many minutes after the arterioles have regained their vascular tone [9 102] This collateral dilatation with its associated augmented blood flow can relieve myocardial ischemia and restore near normal contractility to regions with impaired shortening [9 102] Thus collaterals have muscular walls which respond predictably to the proper pharmacologic agent Additional investigation will undoubtedly uncover other agents with specific effects on coronary collaterals which can then be used clinically

Many attempts to stimulate collateral development have been made but few have any potential therapeutic benefit However daily treadmill running does promote collateral growth in dogs with critical coronary stenoses[1 3] Therefore exercise may be an important part of the long range therapeutic regimen for patients with coronary artery disease

Thus animal experimentation has yielded definite evidence that collateral vessels are functional after an abrupt coronary occlusion Although they are usually unable to prevent infarction the anastomoses do limit the extent of the ischemic process and mortality Once functional the collateral vessel undergoes a tremendous histologic anatomic and physiologic transformation which greatly increases its significance as an alternate route of supply to the ischemic heart Stimulation of collateral flow has tremendous clinical significance and must represent one of the important goals of future investigation Application of the results of animal research must be applied cautiously to any clinical situation and new methods and techniques must be evaluated critically without bias However the results obtained in the experimental setting hold great promise If collateral enlargement and/or growth could be induced either before or immediately after coronary occlusion then the effects of this dreaded coronary event would be significantly attenuated

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between the groups was the initial period during which the hollow plugs were slowly becoming occluded It is postulated that during the pre occlusion period collaterals were stimulated to enlarge so that much of the ischemic myocardium could be metabolically supported following total obstruction In chronically instrumented dogs with gradually progressive coronary occlusions, changes in collateral indices including retrograde coronary flow and xenon clearance from the ischemic region support the assumption of increased collateral flow prior to complete obstruction [82]

Effect of time on development Temporal changes in collateral flow following acute coro nary obstruction have been investigated by multiple techniques Alterations in xenon clear ance and thermal conductivity in the ischemic region have been inconsistent However Pasyk and co workers[83] have documented increases in the indices of collateral flow in instrumented dogs 20 to 31 hours following acute left circumflex artery obstruction With flowmeters implanted around the distal portions of occluded vessels, Elliot and associates[82, 84] were able to identify collateral flow patterns within six to eight hours following occlusion The use of radioactive microspheres has permitted quantitation of regional myocardial blood flow to both endo and epicardium at various time intervals following coronary occlusion Marcus and co workers[64] noted a doubling of endocardial and epicardial flow as early as five minutes after coronary occlusion, and a further flow increase at one hour Rivas and colleagues[74] and Smith and co work ers[85] also observed flow to be significantly increased at two hours, although this observation was not confirmed by others [81, 86] Twenty four hours following occlusion, blood flow to the central ischemic tissue is approximately doubled (0 12 to 0 18 [87] 0 12 to 0 29,[81] 0 25 to 0 53 ' ml / min /gm) This increase was observed in both epicardial and endocardial halves Thus blood flow to ischemic areas can increase acutely During the initial 24 hour period, both peripheral coronary pressure and retrograde flow from the ligated vessel increased and collateral conduc tance doubled [87] Besides the increase in blood supply to the ischemic area there is also an internal redistribution Schaper and Pasyk[88] and Hirzel and associates[87] measured flow to the infarcted endocardium and surviving overlying epicardium and noted that flow in the latter appeared to increase at the expense of the forme within the first hour following coronary occlu sion Tissue destined to become necrotic perhaps swells significantly, thus compressing collateral channels and initiating a flow redistribution

Spatial distribution in ischemic tissue Other than temporal distribution of collateral flow spatial distribution is of especial concern to those interested in attempting to attenuate the ravages of myocardial ischemia Although the existence of a border zone of partially ischemic tissue surrounding a central core of deeply ischemic tissue has been claimed by some, others believe that the underperfused area is uniformly ischemic and surrounded by normal myocardium Becker and co workers[93] have documented a tenfold drop in flow from a border zone to the center of the ischemic region with intermediate flows between the two However, before sectioning the heart they failed to specifically identify the ischemic region and therefore could not have avoided including normally perfused tissue in the so-called "border zone ' Domenech [9] carefully out lined the perfusion area of the occluded coronary artery by Evans blue injection and sectioned only the stained areas He described a threefold radial gradient But even this is likely to be an overesti mate, since total exclusion of normal tissue is probably still not possible Fischl and colleagues[90] attempted to account for the amount of normally perfused tissue within the perfusion territory of the occluded vessel and observed that if the truly ischemic tissue was analyzed only a negligible gradient existed Measuring washout of intra myocardial Xe^{133} depots, Linder ' also noted a marked decline in blood flow to 10 per cent of normal within a few millimeters of the border between well perfused and ischemic myocardium, and an additional decrease of only 5 per cent to the central zone Although a definite radial gradient may not be present, blood flow to the ischemic area is probably not homogeneous Analysis of the three dimensional geometry of ischemic myocardium [93] intravenous fluorescein injection studies [66] and histologic examination ' of infarcted tissue reveal relatively well perfused normal appearing myocardium amongst necrotic fibers

If a radial gradient is questioned there is little doubt about a transmural gradient Endocardial flow is severely depressed while epicardial flow is

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Fibrin deposition on a pacemaker catheter in a heparinized patient

Transvenous ri ht ventricular cardiac pacing for disorders of cardiac rhythm has been a recognized clinical tool for a number of years Reports of thrombotic complications involving temporary transvenous pacing catheters are rare

Recently a 35-year-old man was admitted to our coronary care unit with an inferior myocardial infarction On the first hospital day 7,500 units of heparin was begun and continued every four hours sufficient to produce slightly prolonged partial thromboplastin times 3 5 hours after each dose During the second hospital day progressive A V block necessitated the placement of a temporary transvenous right ventricular pacemaker A Cordis bipolar pervenous electrode (Catalog number 3/0-110) was positioned in the right ventricl via a left median antecubital venous cut-down The pacemak r functioned well for eleven days with only minimal increase in milliamperage When the pacemaker was removed a thin layer of tissue 1 to 2 mm in thickness was observed tightly adherent to the catheter and partially encircling it It began 6 cm from the catheter tip and extended proximally 6 cm Pathologic examination of the thrombus r vealed it to be 1 to ? mm in thickness with the greatest density in the proximal portion It was friable and had a laminated appearance Microscopically there were strips of fibrin alternating with layers of cells mainly neutrophils The area directly adherent to the catheter was acellular In several areas on the external surface of the thrombus flattened endothelial like cells were seen (Fig 1) Trichrome stain revealed no evidence of collagen

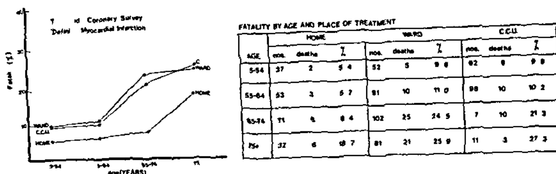
Surface thrombus deposition on intravascular devices has been reported involving Swan Ganz Catheters central venous pressure catheters, and transvenous pacemakers Goldberg described a single patient with a right ventricular thrombus at the catheter pole in a series of 115 patients transvenously paced in excess of one week on no anticoagu lant He concluded that no aggregates of blood elements greater than wispy fibrin clots have been found on any catheter Forrester and associates reported that Swan-Ganz Catheters left in position up to 96 hours in 40 critically ill patients revealed no evidence of thrombus formation Gott reports that heparin over a wide concentration range will not only inhibit the generation of thrombin in plasma but block the action of fibrin on fibrinogen and block platelet agglutina tion by formed thrombin on transvenous catheters Our patient was well heparinized and yet significant thrombus deposition occurred The position of the thrombus formation suggests formation in the right atrium similar to the patho logic findings of Becker and co-workers Thus heparin in full



Fig 1 Thrombotic material stripped from catheter demonstrating laminated appearance (Hematoxylin and eosin original magnification ×250)

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FATALITY BY AGE AND PLACE OF TREATMENT

AGE	HOME nos.	HOME deaths	HOME %	WARD nos.	WARD deaths	WARD %	C.C.U. nos.	C.C.U. deaths	C.C.U. %
5-54	37	2	5 4	52	5	9 6	82	8	9 8
55-64	53	3	5 7	91	10	11 0	98	10	10 2
65-74	71	6	8 4	102	25	24 5	7	10	21 3
75+	32	6	18 7	81	21	25 9	11	3	27 3

Fig 1 Graphic and tabular presentation of deaths from myocardial infarction in the Tees-side survey A comparison is made of deaths occurring at home in the hospital ward and in the coronary care unit

urban population (396 000) in the north-east of England Published results from the survey include details about incidence mortality and fatality of attacks—the schedule of events leading to patients coming under care the frequency and relevance of premonitory symptoms and the fatality rates of patients treated at home and in hospital It is this last aspect that is particularly considered in this annotation I am obliged to my co-authors for their permission to reproduce some of our results

A total of 2 ,71 attacks were reported usually by family doctors, with a positive diagnosis of either "definite" or possible myocardial infarction in 1 938 cases Of these 9 9 patients died within ?8 days of onset of the attack giving an episode fatality rate of 50 5 per cent

During the first 6 months of the survey 4?6 patients died and a detailed scrutiny was carried out of the circumstances of their death. This revealed that for 65 per cent of this group there was either no interval between onset of attack and death or the interval was unknown almost all because the death was unwitnessed

Eighteen per cent of the deaths occurred between onset of attack and 1? hours later It is this rather small group of ,9 cases for whom emergency services like mobile units would be most effective A further 17 per cent died between 1? hours and ?8 days after onset of attack

Cases were classified as treated in this survey only if data (history physical examination ECG cardiac enzymes) for diagnostic assessment had been collected Quite fortuitously patients fell almost equally into three treatment groups. Of the 1 109 patients 374 were treated at home 397 were in hospital wards and 3?4 were in coronary care units (Fourteen patients were excluded because insufficient data were available but none of these patients died)

The restriction of the analysis to assessed cases gave rise to two problems First the interval from onset to assessment was different for different treatment groups Hospital cases were seen fairly consistently between 3 and 4 hours after the attack, but the interval for home patients varied from 2 to 12 hours, according to whether the case was notified during the day or night Second of the 64 patients who died between onset and assessment 63 had been referred to hospital If cases had been admitted to the analysis at the point at which place of treatment had been chosen rather than at the point of diagnostic assessment hospital fatality rates would have appeared much worse

Table 1 Age standardized fatality rates (in per cent) in patients with definite myocardial infarctions by place of treatment

	Home	Ward	Coronary Care Unit (CCU)
Men	7 3	14 8	14.8
Women	9 0	?6 9	17 6

There was no difference between the three groups in terms of shock history rhythm changes and ECG abnormalities. The Peel Index modified to incorporate additional data in this survey was used to assess severity and showed no difference between patients treated in home ward or CCU But there were differences for age (Fig 1) and serum aspartate aminotransferase (SGOT) levels Accordingly the fatality rates given in Table 1 have been standardized for age Further standardization for SGOT levels do not alter the figures appreciably

One major difference between home and hospital treated patients was revealed in th timing of events prior to the patients coming on to treatment In the case of hospital treated patients the call was made to the doctor half an hour earlier than for home treated patients (median times from onset 1 hour and 1½ hours) In addition the doctor reached the patient twice as quickly (median times half an hour and 1 hour) These differences were not related to the mode of onset—sudden or gradual—or to whether the main symptom was pain syncope dyspnea or dysrhythmia

One way of explaining these results would be in terms of the way in which the patient and his family react to the crisis If the family physician is faced with a home situation which conveys panic and alarm he will seek to act decisively and would therefore probably opt for hospital treatment It is this very feeling that decisive action necessarily means hospital that this and other studies have brought into question

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therapeutic doses does not provide absolute protection against thrombus formation on indwelling cardiac catheters In a patient with acute myocardial infarction thrombus formation may occur and could act as a source of pulmonary embolic disease despite adequate heparin therapy

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Of diastolic and systolic pressure and left ventricular work

The usual opinion in clinical medicine is that the level of the diastolic pressure is more important than the level of systolic pressure and that the higher the diastolic pressure (DP) the greater the work of the left ventricle (LV) There is a tendency to ignore the systolic blood pressure (SP) and the pulse pressure (PP) is rarely ever even mentioned But when the aortic valve is functioning normally the diastolic pressure in the aorta and arterial system does not impose its load upon the LV This pressure is supported by the aortic valve cusps during ventricular diastole when the cavity of the left ventricle is isolated from the arterial system and its intraluminal pressure However as the LV contracts and raises intraventricular pressure to a level that just exceeds the pressure in the aorta the aortic cusps open and the cavity of the LV and the arterial system become continuous The ventricle continues to contract to reach its maximal pressure level which is systolic pressure The systolic pressure and the time course of pulse pressure then determine the level of the maximal pressure load imposed upon the LV The length of time that the aortic cusps are opened determines the duration during which pulse pressure and systolic pressure are imposed upon the LV wall The integral of the time course relationship of the intracavitary pressure of the left ventricle to left ventricular volume during a cardiac cycle reflects the time course of work of the left ventricle per heart beat Thus as indicated a number of years ago the time course of the pressure-volume relationship of the left ventricular cavity defines the time course of LV work and also determines the time course of tension of the left ventricular wall However the systolic pressure as well as diastolic pressure determines the time course of work and tension The systolic pressure and time course of pulse pressure must receive serious consideration in cardiology

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At home or to hospital?

The possibility that an acute serious illness might be better treated at home would seem to be contrary to orthodox medical thinking Yet there are pointers and they are more than just straws in the wind to suggest that in the case of acute myocardial infarction many of the sufferers would be better off treated in the familiarity of their own home

One such pointer comes from a survey of attacks of acute myocardial infarction occurring in a 12 month period in an

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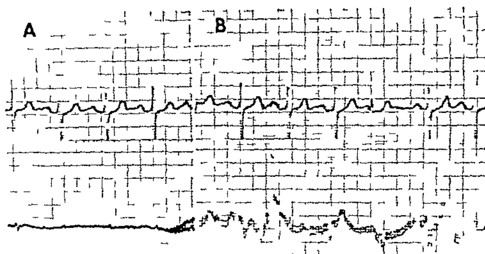


Fig 2 Dynami electrocardiogram of patient 2. Channel one *above* channel two *below* *A* During waking hours *B* While under the electric blanket

sleep under an electric blanket during the time of continuous 24 hour electrocardiography to avoid this interference

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Electromagnetic interference in dynamic electrocardiography caused by an electric blanket

Although numerous causes of artifacts in dynamic electrocardiography have been noted we are unaware of reports of electromagnetic interference as a cause of artifact A recently observed example of this type of interference is described here

A 49 year old white female with a diagnosis of idiopathic ventricular tachycardia had 24 hour dynamic electrocardiography with an Avionics Model No 425 electrocardiocorder An Avionics Dynamic Electrocardioscanner 660 was used in analysis of the 24 hour tape During the sleeping hours there was marked 60 Hz interference that made both channels of the printout uninterpretable (Fig 1) During a 30 minute period when the patient arose from sleep this interference completely cleared We looked for possible causes of this electromagnetic interference and found the patient had slept under an electric blanket To see if the electric blanket was the cause of the interference two other Holtered subjects slept under an electric blanket As noted in Fig 2, one channel of the ambulatory electrocardiogram showed marked electrical interference during this time Patient 3 (not illustrated) also slept under an electric blanket and although the electrocardiogram was easily interpretable 60 Hz interference was noted on one channel at periodic times during the night In all three of these patients dynamic electrocardiograms during the remainder of the time were technically adequate tracings

Our conclusion is that electric blankets can interfere with the electrocardiogram recorded during dynamic monitoring This interference may render a considerable portion of the monitoring uninterpretable and therefore decrease efficacy of Holter monitoring We would recommend that patients not

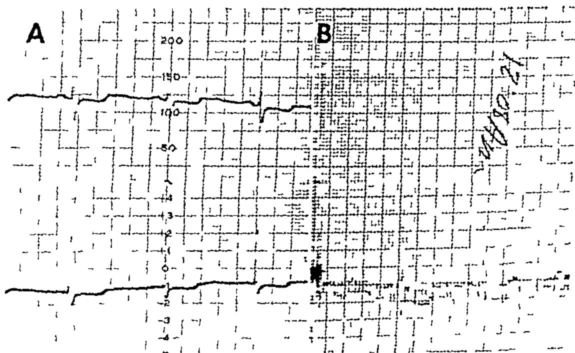


Fig 1 Dynamic electrocardiogram of patient 1 Channel one *above* Channel two *below* *A* During waking hours *B* While under the electric blanket

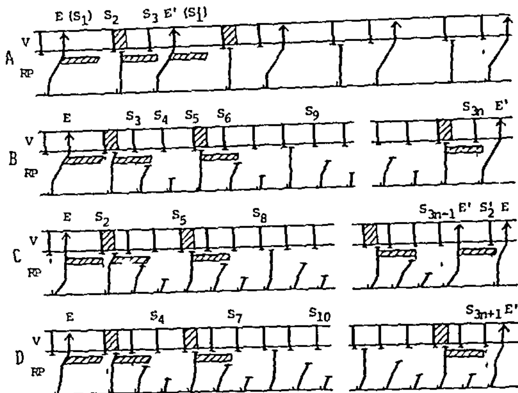


Fig 1 Strips illustrating a manifest trigeminy *(strip A)* and a classical form *(strip B)* and two variants *(strips C and D)* of concealed trigeminy Shaded areas represent the refractory period. Intraventricular conduction of the sinus impulse leading to the re-entry path is indicated by dashed lines Conduction in the re-entry path for the extrasystolic impulse re-entering into the path is not indicated here because the conduction appears to be blocked at a proximal site of the re-entry path and bring about no significant effect on the next sinus impulse conducted into the path. E = extrasystole S and *(S)* = sinus impulses conducted and non conducted to the ventricles respectively V = ventricles *RP* = re-entry path

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Reply

To the Editor

In patients with frequent extrasystoles, it is not possible at present to record the electrical activity directly from the ectopic focus or reentry loop When the extrasystoles occur in certain regular patterns, critical analysis of such patterns may provide some insight into the underlying electrophysiological mechanisms

The mechanisms we have proposed in a recent issue of this journal to account for classical concealed trigeminy and two of its variants are consonant with known electrophysiological phenomena The mechanisms proposed by Dr Kinoshita are also feasible It is certainly not possible to choose between the two alternatives with certainty nor to rule out still other reasonable possibilities

Our preference for the hypothesis outlined in our paper was guided in part by the fact that the extrasystoles were late and many fusion beats were seen This is clearly illustrated in our Fig 5 which depicts our concept of the mechanism for the classical form of concealed trigeminy Extrasystole R follows two conducted sinus beats (S = 2) and it begins near the peak of a P wave It is followed by five more conducted sinus beats (S = 5) Had the conduction time around the reentry loop after sinus beat R been slightly greater an extrasystole would not have been manifest after R i e the reentrant impulse would have been concealed by virtue of interference" Consequently there would have been eight conducted sinus beats (S = 8) in the interectopic interval between R and R S = 2 5 and 8 conducted sinus beats are all compatible with the

Letters to the Editor

Mechanism of concealed trigeminy

To the Editor

I have read with great interest the report by Dr Levy and colleagues on two variants of concealed trigeminy In 1960[2] before Schamroth and Marriott, we reported a case showing the phenomenon of classical concealed trigeminy namely that sinus impulses intervening between two successive ventricular extrasystoles were generally in multiples of three (3n where *n* is any positive integer) The sinus impulses here include those both conducted and nonconducted to the ventricles Before seeing the cases of Dr Levy and colleagues[1] we had also believed their assumption namely that in all cases of classical concealed trigeminy 3 1 exit block occurs at the same site in the re entry path indicating that the refractory period of this site is longer than twice the sinus cycle though it is shorter than three times the sinus cycle At the present time however I think that some cases of classical concealed trigeminy may be governed by another mechanism In this letter I would like to offer possible explanations for the cases of Dr Levy and colleagues which are different from those postulated by them

It seems to me that their cases of concealed trigeminy are a *variant of 3 2 Wenckebach exit block due to concealed* conduction into the re entry path The mechanism is illustrated by diagrams in Fig 1 The longest refractory period in the re entry path here is shorter than twice the sinus cycle The refractory period is represented by shaded areas

Strip A shows a (manifest) trigeminal rhythm which occurs in a comparatively slow sinus rhythm The first sinus impulse (S_1) following the manifest extrasystole *E* is blocked at the atrioventricular (A V) junction Thereafter the sinus impulse S_2 conducted to the ventricles falls long after the refractory period of the re entry path As a result it reaches the distal end of the path without enough delay and becomes a concealed extrasystole due to interference On the other hand the next conducted sinus impulse S_3 falls shortly after the refractory period of the re entry path so that it reaches the distal end of the path after marked delay and becomes a manifest extrasystole *E* The sinus impulse (S_1) subsequent to the extrasystole *E* is again blocked in the A V junction This phenomenon is similar to 3 2 Wenckebach exit block though a block recovering conduction of the next sinus impulse occurs in the A V junction The presence of such a trigeminal rhythm was indicated in my previously reported patients with a variant of concealed bigeminy

Strip B shows a classical concealed trigeminy caused by a variant of 3 2 Wenckebach exit block The sinus rate is somewhat rapid as compared with that in *strip A* Therefore the sinus impulse S_3 subsequent to a concealed extrasystole due to interference is blocked at some site in the re-entry path (site A) after it invades markedly slowly a considerably large part of the path In other words it becomes a concealed extrasystole due to exit block As a result the next sinus impulse S_4 is blocked at another site in the path (site B) which is proximal to site A Namely block (not interference) of the sinus impulses here occurs at two different sites in the re entry path After a block at the proximal site B the sinus impulse S_5 again passes through the re entry path without enough delay and becomes a concealed extrasystole due to interference In the A V junction such a variant of 3 2 Wenckebach block due to concealed A V conduction has been indicated for example in patient 27 displaying 3 1 A V block that is recently reported by Kosowsky and associates (their Fig 7)[4]

The terminal part of *strip B* shows that when the sinus cycle somewhat lengthens a sinus impulse following a concealed extrasystole due to interference i e the impulse S_3 falls shortly after the refractory period of the path and again *becomes a manifest extrasystole E Thus the number of the* interectopic sinus impulses becomes a multiple of three

In Case 1 of Dr Levy and colleagues too such long sinus cycles favored the appearance of extrasystoles during classical concealed trigeminy The same feature has been disclosed in some variants of concealed bigeminy [3] In Cases 2 and 3 of Dr Levy and colleagues bigeminal rhythm occasionally occured These findings strongly suggest that the refractory period of the re-entry path in their cases is shorter than twice the sinus cycle

Strips C and D illustrate two variants of concealed trigeminy in which the sinus rate is more rapid than that in *strip B* though the refractory period of the re entry path remains shorter than twice the sinus cycle As a result of such a rapid sinus rate conduction in the re entry path is considerably delayed even in the region proximal to site B Thus when in *strip C* showing one of the variants the sinus rate is increased beyond a certain critical value (CR) the sinus impulse S_{3n-1} gives rise to a manifest extrasystole *E* despite the fact that this impulse falls long after the refractory period of the distal site (site A) On the other hand when in *strip D* illustrating the other variant the sinus rate is increased beyond another critical value (CR) the sinus impulse S following a concealed extrasystole due to interference is blocked at the proximal site (site B) before occurrence of the variant shown by *strip C* As a result the next sinus impulse S_{3n+1} falls comparatively shortly after the refractory period of site A resulting in a manifest extrasystole *F* In cases in which CR is lower than CR_1 the variant illustrated by *strip C* occurs in which the numbers of interectopic sinus impulses are multiples of three minus 1 ($3n - 1$) indicating Cases 2 and 3 of Dr Levy and colleagues Conversely in cases in which CR is lower than CR the variant illustrated by *strip D* occurs in which the numbers of interectopic sinus impulses are multiples of three plus 1 ($3n + 1$) indicating their Case 1

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Reply

To the Editor

We thank Dr Puech for calling our attention to his previously reported excellent work concerning recording of left atrial activity from the pulmonary artery *It appears that* we have rediscovered that which is already known We therefore give priority to Dr Puech for his original observations. We are pleased to be able to confirm his previous work

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Preceptorships at major medical centers

To the Editor

I want to endorse the recommendation of Dr Myron R Schoenfeld in the AMERICAN HEART JOURNAL of May 1977 page 6 6 I would agree that the only satisfactory solution for the physician surgeon to learn new techniques is to have practical experience at a major medical center and it would seem a short Preceptorship would be an excellent method

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Sudden deaths from IHD by age and sex

To the Editor

Several studies have reported that the percentage of *sudden deaths is higher for* younger men than for older men This has also been contradicted I have recently studied all 19 2 deaths from ischemic heart disease (International Classification of Disease 8th ed., No 410-414) in Vermont. This was a year in which there were very few deaths from influenza *All coding was done by the same person at the* Vermont State Health Department When there was more than one cause of death listed on the certificate the *underlying cause* as determined by a physician was coded

Each death certificate was individually read and information *was recorded* on age sex, and interval between onset of terminal episode and death Criteria similar to those suggested by Gillum and associates were used to *determine eligibility* There were 1 464 deaths in the 410-414 category but for various reasons such as death caused by stroke death in *surgery death caused* by sepsis, etc 50 cases were rejected making the number studied 1 414 Of these 1 414 cases interval information was available on 81 4 *per cent* or 1 151 cases.

I have found that younger males and females have a higher percentage of sudden deaths than older males and females

Table 1 *Per cent sudden deaths (up to 1 hour) from IHD by age and sex Vermont 1972*

	Age (years)					
	30-45	*46 55*	*56 65*	*66 75*	*76 85*	*Over 85*
Male	40	72	56	45	49	29
Female	32	74	54	42	33	21

Inherent here is the problem of correctness of the death certificates. Gillum and colleagues found in 56 cases of IHD deaths in Framingham that death certificates were correct 70 per cent of the time in determination of sudden death using 1 *hour as a definition of sudden death* Thus it is probable that the data presented here may not be totally correct but nevertheless the over all trend is impressive

Recently a historical prospective study on the relationship between ventricular premature contractions on routine ECG and subsequent death from coronary heart disease was performed on North Carolina factory workers The authors used *death certificates as the sole source of information to* establish cause of death and to divide the interval between onset of symptoms and death into 1 hour sudden deaths 24 hour sudden deaths, and non sudden deaths.

Since deaths in younger persons are the most premature and therefore the most important to prevent it would seem worthwhile to study this situation further Thank you

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existence of classical concealed trigeminy ($S = 3n - 1$ where n is any positive integer)

The mechanism proposed by Dr Kinoshita involves critical changes in the sinus cycle length In our Fig 1 the sinus cycle lengths immediately after each of the two extrasystoles in the top strip are less than the sinus cycle length after the first extrasystole in the second strip This longer cycle in the second strip is followed by another extrasystole after only two conducted sinus beats (S = 2) In the top strip however S = 5 after each of the extrasystoles The shorter sinus cycle lengths immediately after the extrasystoles in the top strip are consonant with Dr Kinoshita s hypothesis for a manifest extrasystole did not appear after these short cycles i.e., after the second sinus R wave Presumably the extrasystoles after the second sinus R waves in both interectopic intervals in the top strip were concealed However the sinus R R intervals that followed immediately after the second extrasystole in the second strip (S = 5) and after the first extrasystole in the third strip (S = 11) were not detectably shorter than the first sinus R R interval in the second strip (S = 2) On the basis of Dr Kinoshita s theory one might therefore have expected manifest extrasystoles after the second sinus R wave that followed the second extrasystole in strip 2 (instead of after the fifth R wave) and after the second sinus R wave that followed the only extrasystole in strip 3 (instead of after the eleventh R wave)

Precise measurements of electrocardiograms from a larger series of patients will undoubtedly provide a more secure basis for unraveling the mechanism responsible for these fascinating arrhythmias Rational hypotheses such as those proffered by Dr Kinoshita provide the cardiologist with a logical frame work with which to guide such critical measurements Such analyses will lead to modifications of the existing hypotheses and successive modifications should more closely approximate the truth

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Indirect recording of left atrial activation in the main pulmonary trunk

To the Editor

In the March 1977 issue of this JOURNAL Amat y Leon and colleagues give a beautiful example of left atrial recording by positioning an electrode catheter in the main pulmonary trunk We share their opinion on the interest of this supplementary way of exploring left atrial activity more precisely that of the left atrial appendage when the tip of the electrode catheter is close to the left border of the pulmonary artery

We used this new approach more than 20 years ago many

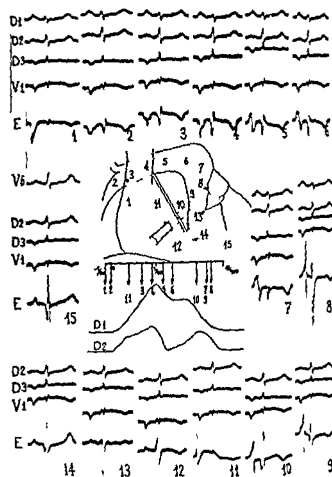


Fig 1 Intracavitary mapping of the atrial activation in a case of left atrial enlargement (mitral stenosis)

examples of atrial mapping including atrial electrograms recorded in the pulmonary artery were obtained in normal and pathological cases and were illustrated in the old books dedicated to intracardiac electrocardiography Fig 1 is a representative example of atrial mapping performed with unipolar electrodes The modern use of bipolar electrograms for timing atrial depolarization is undoubtedly more accurate

We congratulate Dr Rosen s group for informing the English speaking readers about this third alternative to the indirect exploration of the left atrium in addition to esophageal and coronary sinus leads which must be considered for clinical applications in cases of ectopic atrial activation

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Qual ty Control in Nuclear Med c ne Radiopharmaceut cals Instrumentat on and In V tro Assays Edited by Buck A Rhodes St Louis 1977 The C V Mosby Company 455 pages Price $39 50

Local Anesthet cs 2nd edition By Rudolph H de Jong M D Springfield Ill 1977 Charles C Thomas Publisher 275 pages. Price $32.50

Pathophysiology and Therapeut cs of Myocardial Ischemia Edited by Allan M Lefer Gerald J Kelliher and Michael J Rovetto Jamaica N Y., 1977 Spectrum Publications, Inc., 530 pages Price $38.50

The Prostaglandins vol 3 Edited by Peter W Ramwell New York 1977 Plenum Publishing Corp 347 pages. Price $39 50

Guide to Fitness after 50 Edited by Raymond Harris M D., and Lawrence J Frankel, New York, 1977 Plenum Publishing Corp 338 pages Price $24 50

Rheology of Blood in Diagnostic and Preventive Medicine By Leopold Dintenfass London 1976 Butterworth & Co Ltd 396 pages Price $27 95

Physicians including cardiologists and vascular physicians and surgeons give relatively little consideration to rheology of blood They fail to even realize the importance of blood viscosity in peripheral blood flow The hydraulic and hemodynamic aspects of the circulation must be borne in mind constantly when treating patients with cardiovascular disease This is particularly true for the peripheral and coronary circulations Readers will appreciate this better from Dintenfass book on clinical hemorheology The author has written this book for practicing physicians The book contains discussion of hemodynamic phenomena of rheology in ischemic heart disease sickle cell anemia and other hematologic disease states senility and various hyperviscosity states of the blood This book is excellent It focuses attention on aspects of the circulation that require much more attention such as the role of viscosity in renal disease Maybe the anemia associated with renal disease is advantageous This reviewer thinks the low viscosity of anemic blood could be a definite advantage under certain circumstances Thus with further thought readers can advance their therapeutic considerations of disease states in their patients The bibliographies are very good Dintenfass has added an important book to the medical literature This book is highly recommended to all trainees in medicine especially those training in the cardiovascular fields

The Essentials of Cardiac Pacing By G Fontaine Y Grosgogeat and J J Welti London 1977 William Heinemann Medical Books Ltd 77 pages

This relatively inexpensive paperback book on pacing presents in simple and lucid manner the problems of cardiac pacing The illustrations are simple and clear The presentation is intended for physicians nurses and other attendants who are involved in the CCU and cardiac programs of hospitals The translation from French to English is not only good but welcome since the book will reach many more readers Indications technics complications functional problems prognosis and follow up procedures are among the many phases of cardiac pacing discussed This is a good and concise book on the subject It is easy to read and obviously written by experienced French physicians

Acute Myocardial Infarction Reaction and Recovery By Rue L. Cromwell Ph.D Earl C Butterfield Ph D Frances M Brayfield M.A and John J Curry M D Saint Louis 1977 The C V Mosby Company 224 pages Price $10 50

Cromwell and associates have produced a book of little over 200 pages for nurses doctors and others concerned with the care of patients with acute myocardial infarction The psychologic impact that this acute medical emergency has on the sufferer is too often forgotten by the busy attendants Certainly a well trained and experienced physician is aware of his patient s reaction to his illness but others too often fail to realize this aspect of the care of the patient The complex equipment of the CCU demands so much attention that the patient receives inadequate attention and concern for his psychologic state and reaction to the illness and his surroundings This book discusses the importance of the patient s psyche and reviews the results of studies of the patient s response to doctors nurses and other attendants as well as to his surroundings The psychologic assessment of the coronary patient and the manner of coping with his reactions to the CCU the apparatus and people are reviewed The study was conducted in large part at the Holy Cross Hospital in Silver Spring Maryland with John Curry providing the cardiologic support This is an interesting book for nurses and trainees in medicine Even the well trained experienced physician should find the investigations and recommendations interesting and stimulating even though a great deal is already well known to him.

Patient Care in Cardiac Surgery second edition By Douglas M Behrendt M D and W Gerald Austen M D Boston 1976 Little Brown & Company 179 pages

This is a very useful condensed source of practical information concerning the care of the cardiac surgical patient The advancements in complex cardiac surgery have introduced equally complex and important procedures and practices related to pre operative operative and post operative care of the cardiac surgical patient This small book describes in a brief manner the essentials for the surgical care of adults and children undergoing operations on the heart The illustrations are well chosen and clear The use of outlines tables and charts is a good feature of this book The authors emphasize their own experience and include those of others Cardiologists who participate in the care of cardiac surgical patients will find the book informative and a fine and helpful source of informaton on drugs as well as procedures This second edition is highly recommended to cardiologists as well as to cardiac surgeons

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American Heart Journal

April 1978 Volume 95 Number 4

Editorial

Natural fibrinolysis

Norman L Browse M D F R C S (Eng)
London England

When prehistoric man cut himself and saw the cut seal up with congealed blood he probably appreciated that this was a life saving property of the blood but thousands of years passed before Morgagni and Hunter[1] observed that there was a natural system in the blood which could prevent its coagulation The intricacies of the coagulation mechanism have been gradually unravelled over the past three decades but we have been far less successful in expanding our knowledge of the fibrinolytic system In 1937 Macfarlane[3] demonstrated that test tube thrombi made from blood taken during surgical operations sometimes dissolved spontaneously and in 1953 Fearnley and Tweed showed that there was some fibrinolytic activity in the blood of patients at rest At the same time Mole[5] and Kwaan and McFadzean[6] developed the hypothesis that the vascular endothelium was the main source and store of fibrinolytic activator which was confirmed when Todd[7] demonstrated an activator of fibrinolysis in the walls of small blood vessels particularly the veins and Astrup showed that there are plasminogen activators in almost all of the fluids and tissues of the body

As our knowledge has progressed two hypotheses have developed The first is that fibrinolysis exists as a counterbalance to thrombosis by dissolving the many small thrombi which may develop in the circulation and so keeping the blood liquid The second is that an abnormality of natural fibrinolysis might predispose towards intravascular thrombotic disease particularly in the veins or exacerbate the deposition of fibrin in atherosclerosis and any other condition associated with a fibrinous exudate

Hard evidence that fibrinolysis and coagulation maintain a balance which keeps the blood liquid is circumstantial and sparse There is no doubt that both systems exist and that abnormality of one or the other leads to pathological states but no one has clearly demonstrated a continual intravascular deposition of fibrin which is continually being dissolved by fibrinolysis

The association between a deficiency of fibrinolysis and vascular disease is becoming more apparent After Fearnley s original studies of natural fibrinolysis he searched for drugs which might enhance fibrinolytic activity and found that the combination of an hypoglycemic drug such as phenformin and an anabolic steroid such as ethylestranol would produce long term enhancement of blood fibrinolytic activity[9] He postulated that these drugs might be used for the treatment of arterial venous and inflammatory diseases In Malmo Inga Marie Nilsson and co workers[10,11] extended these studies and showed that there was an abnormality of tissue fibrinolytic activator in patients with venous thrombosis and that recurrent thrombosis associated with an abnormality of fibrinolysis could be prevented by pharmacological fibrinolytic enhancement

Browse and associates[2] at St Thomas Hospi

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Received for publication June 28, 1977

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Announcements

William Harvey 400th Anniversary Celebration

A conference celebrating the 400th anniversary of the birth of William Harvey will be held July 9 through 13 1978 at the Royal College of Physicians of London This conference will include a two and a half day symposium entitled Modern Methods of Studying the Circulatory System For further information regarding this conference please contact Conference Secretary Harvey Celebration 1978 Royal College of Physicians Regents Park London NW1 4LE England

Fifth European Congress of Anesthesiology

The Fifth European Congress of Anesthesiology entitled Hemodynamics in Anesthesia and Intensive Care will be held in Paris France on September 4 through 9 1978 in the Palais des Congrès For further information regarding this congress please write Congres Anesthesie–P M V B P 916 92205 Neuilly Sur Seine France

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following statement signed by each author 'The undersigned author(s) transfers all copyright ownership of the manuscript entitled (*title of article*) to The C V Mosby Company in the event the work is published The author(s) warrants that the article is original is not under consideration by another journal and has not been previously published Authors will be consulted when possible regarding republication of their material

M Blood and vein wall fibrinolytic activity in health and vascular disease Br Med J 1 478 1977
13 Jarrett, P E M Morland M and Browse N L. Idiopathic recurrent superficial thrombophlebitis Treatment with fibrinolytic enhancement Br Med J 2 933 1977
14 Burnand K G Clemenson G Whimster I and Browse N L Extravascular fibrin deposition in response to venous hypertension—the cause of venous ulceration Br J Surg 63 660 1976
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tal London have recently published a review of a large series of patients with various forms of vascular disease which suggests that there are two degrees of natural fibrinolytic inactivity Arm vein blood from patients with atherosclerosis, Raynaud s syndrome secondary to scleroderma, or a past history of deep vein thrombosis has a depressed fibrinolytic activity but a normal level of activity after ten minutes of venous congestion, whereas blood from patients with idiopathic recurrent superficial thrombophlebitis or post phlebitic lipodermatosclerosis has depressed activity at rest and after venous congestion

These workers have also conducted a number of clinical trials of fibrinolytic enhancement which appears to confirm the hypothesis that some of these diseases or their symptoms are due to the abnormality of blood fibrinolytic activity, because the correction of the blood abnormality has cured the symptoms For example, in 16 patients with idiopathic recurrent superficial thrombophlebitis the remission of symptoms was directly related to the correction of blood activity [13] This variety of recurrent thrombosis was studied rather than deep vein thrombosis because it is very difficult to be certain whether patients who have had a deep vein thrombosis and then get recurrent episodes of pain and discomfort are actually having recurrent thrombosis, whereas attacks of superficial thrombophlebitis are easy to see and measure

Perhaps more interesting than the response of the patients with superficial thrombophlebitis is the response of the patients with post phlebitic lipodermatosclerosis The St Thomas group have shown that the changes in the skin and subcutaneous tissues which often accompany damage to the calf muscle pump is probably caused by the deposition of fibrin in the pericapillary spaces which by forming an impervious cuff stops oxygen diffusion to the tissues and ultimately causes tissue necrosis i e, venous ulceration [14] In a small pilot study on 14 patients, presented in a preliminary communication to the Surgical Research Society the enhancement of these patients depressed blood fibrinolytic activity with the anabolic steroid stanozolol produced considerable relief of symptoms and a reduction of the area of tenderness redness induration and pigmentation [15] A double blind cross over trial not yet published has confirmed these results The significant point is that the enhancement of fibrinolysis in these patients appears to be affecting an extravascular abnormality This forces one to consider the possibility that a low level of blood fibrinolytic activity may be an indication of a defect of tissue fibrinolysis and not necessarily a primary blood abnormality It may be that one of the important functions of fibrinolysis is to keep the tissues rather than the blood vessels clear of unwanted protein such as fibrin It is not a new suggestion that there may be tissue clearing proteolytic enzymes [16] If this is the case and if what we measure in the blood and call natural fibrinolysis is simply the spill over of tissue fibrinolytic activity, we must review the hypothesis that the primary role of fibrinolysis is to counterbalance coagulation

All these theories need further detailed investigation after we have refined our methods of measuring blood and tissue fibrinolytic activity But more pressing is the need for new drugs which will produce a greater enhancement of fibrinolytic activity and which are safe for long term administration If such drugs were available we might be able to cure patients with recurrent venous thrombosis, enhance the spontaneous resolution of thrombosis and perhaps reduce the complications of arterial disease by reducing the quantity of fibrin that is laid down in and around atherosclerotic plaques

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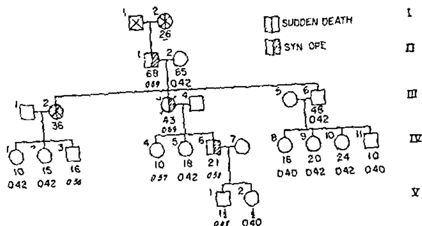


Fig 1 Family pedigree The subjects age in years and Q T interval in seconds are shown beneath their symbol *Abnormal Q T intervals are indicated in italics*

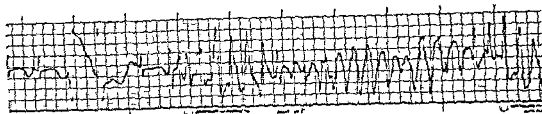


Fig 2 Coronary care unit rhythm strip in propositus III 3 showing onset of ventricular tachycardia which eventually resulted in a typical syncopal episode

hereditary disorder disclosed no significant abnormalities suggestive of a cause of death Her son IV 6 has experienced multiple syncopal episodes since age 6 His Q T interval and that of one of his children is abnormally prolonged Two other family members are affected but asymptomatic—her nephew IV 3 and her daughter IV 4 Her brother III 6 and his four children are unaffected and asymptomatic

Estimation of serum potassium magnesium and calcium values in all living family members were within normal limits

Methods

Informed consent was obtained from all subjects Three affected family members were studied Two were symptomatic II 1 age 68 and IV 6 age 20 and one was asymptomatic IV 3 age 16 A pool of five male and three female volunteers ages 24 to 39 years served as control subjects Four unaffected family members IV 1 IV 2 IV 9 and IV 11 were given atropine and propranolol as described below No subject was receiving any medication at the time of study

The study was carried out on two successive days On the first study day the subjects were brought to the laboratory at 8 A M in the preprandial state In the supine position the following maneuvers were performed (1) manual right and then left carotid sinus stimulation for 7 seconds (2) Valsalva maneuver with the subject expiring against an aneroid manometer to maintain a constant pressure of 30 mm Hg for 15 seconds[6] (3) sustained handgrip[17] at 30 per cent of maximal tension for 3 minutes (4) maximal treadmill exercise using a modified Bruce protocol consisting of 3 minute stages After the heart rate was constant for 15 minutes propranolol hydrochloride was given by intravenous bolus injection in a dosage of 0 15 mg/Kg and the above maneuvers were repeated usually in the course of one half hour Atropine was then administered as a bolus injection in a dosage of 0 035 mg/Kg The maneuvers were again repeated with the exception of treadmill exercise for the affected family members On the second study day the isoproterenol hydrochloride infusion rate (1 mg/1 000 c c) required to increase the resting heart rate by 30 cycles/minute was determined After return to the baseline heart rate the previously calculated dose of atropine was given by intravenous bolus injection and the

Autonomic maneuvers in hereditary Q-T interval prolongation (Romano-Ward syndrome)

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The syndromes associated with hereditary Q T interval prolongation are characterized by a family history of sudden death and syncopal episodes due to paroxysmal ventricular arrhythmias [1-11] When associated with congenital deafness and autosomal recessive inheritance, it is known as Jervell Lange Nielsen syndrome[1] when the pattern of inheritance is autosomal dominant and no deafness is present, the syndrome is termed Romano Ward [4-6]

The relative rarity of these syndromes has rendered it difficult to conduct systematic investigations of etiologic mechanisms At the present time, asymmetric stimulation of the heart via the right and left sympathetic chains appears to hold the most promise as a primary etiologic factor Evidence for this hypothesis includes experimental studies in dogs by Yanowitz and colleagues[12] showing prolongation of the Q T interval by right stellate ganglionic section or left stellate stimulation associated with predominant prolongation of functional refractory period over the anterior ventricular surface amelioration of pharmacologically intractable ventricular arrhythmias in affected patients by left stellectomy[11, 13, 14], and the putative efficacy of beta adrenergic blockade in alleviating symptoms in affected subjects [7, 11, 15]

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This study was performed during Dr Richard Heibel s tenure as a Fellow in Cardiology

Since it appears likely that asymmetric sympathetic stimulation should result from a relative predominance of left chain sympathetic activity its genesis may lie in either increased left or decreased right sided stimulation Schwartz and co workers [11] in a recent review of the literature have proposed the latter is suggested by the many reports of resting sinus bradycardia and exercise induced Q T interval prolongation and some reports of decreased or absent heart rate increments with exercise and atropine administration

Since systematic employment of autonomic maneuvers and autonomically active drugs might serve to uncover autonomic dysfunction in hereditary Q T prolongation we undertook such a study in a family with Romano Ward syndrome

Family history

The propositus III 3 (Fig 1) is a 43 year old white female with a 12 year history of syncopal episodes These episodes were the result of paroxysmal ventricular tachycardia and fibrillation (Fig 2) During sinus rhythm the Q Tc was abnormally prolonged to 0 69 seconds Cardiac catheterization studies including selective coronary arteriography disclosed no abnormalities Sequential blockade of the right and left stellate ganglia by percutaneous lidocaine infiltration was sufficient to produce an appropriate ipsilateral Horner s syndrome but resulted in no alteration of Q T interval The patient was placed on propranolol with an initial decrease in syncopal episode frequency after eight months however the frequency increased necessitating substitution of propranolol by procainamide

Sudden death syncope or abnormal Q T interval prolongation was found in five generations of her family Her grand mother died suddenly at the age of 26 The father II 1 has had multiple syncopal attacks since age 64 and manifests Q T interval prolongation Her sister III 2 died suddenly at age 36 preceded by two months of recurrent syncopal episodes postmortem examination conducted without knowledge of a

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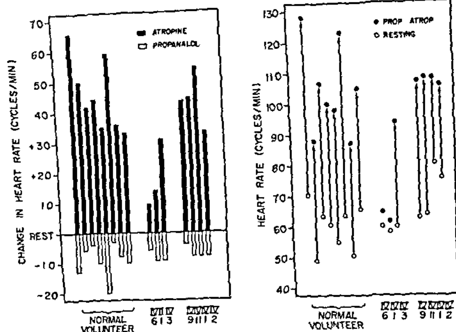


Fig 4 *Left hand panel* heart rate responses to propranolol and atropine in normal volunteers, affected (IV 6 II 1 and IV 3) and unaffected (IV 9 IV 11 IV 1 IV 2) family members The atropine heart rate increment is abnormally reduced in the symptomatic family members (IV 6 IV 1) *Right hand panel* resting and intrinsic (propranolol plus atropine) heart rates in the above subjects The latter rate is abnormally low in the symptomatic family members.

mean increment in heart rate from the beginning of Stage II to the end of exercise was 80 cycles/minute in the normal volunteers and not appreciably different for the affected family members Following beta adrenergic blockade the maximal heart rate achieved and above heart rate increment were significantly depressed in the normal volunteers However the corresponding values were significantly lower in all the affected family members the low increments were not related to a higher heart rate at the onset of Stage II nor to any difference in exercise duration from the control state In the normal volunteers the maximal heart rate achieved following propranolol plus atropine was 4 ± 8 (S D) cycles/minute greater than that observed during beta adrenergic blockade alone this difference was not statistically significant (paired data)

Following beta adrenergic blockade in the normal volunteers decrements in resting heart rate ranged from 3 to 20 cycles/minute and were not appreciably different in the affected and unaffected family members (Fig 4 left hand panel) However following atropine administration the increment in heart rate was grossly abnormally small in the two symptomatic patients The mean heart rate increment in the normal volunteers was 46 cycles/minute (range 33 to 66) in II 1 and IV 6 the observed values were 14 and 9 cycles/minute respectively As compared to the volunteers the atropine increment was also depressed when parasympathetic blockade was preceded by beta adrenergic blockade

The abnormally low heart rate increment with atropine in the two symptomatic subjects was not related to elevated resting heart rates All three affected family members tended to have low resting heart rates averaging 61 63 and 60 cycles/minute for II 1 IV 6 and IV 3 respectively The intrinsic heart rate or the heart rate recorded five minutes after combined beta adrenergic and parasympathetic blockade was significantly depressed in the symptomatic members (Fig 4 right hand panel) The observed values of 58 and 64/minute were 10 and 27 cycles/minute below the lower limit of normal expected on the basis of age Control left ventricular systolic time intervals of the symptomatic family members were well within normal limits and after combined blockade their PEP/LVET ratios were similar to that found in normal volunteers In addition the heart rate observed after ganglionic blockade was abnormally low (Fig 5) For II 1 and IV 6 the values observed were 64 and 63 cycles/minute in normal volunteers previously studied in our labo

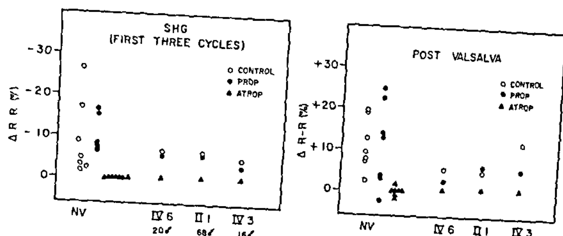


Fig 3 Heart rate responses to sustained hand grip (*SHG left panel*) and Valsalva release in the normal volunteers (*NV*) and affected family members *Atrop* = atropine *Prop* = propranolol

Table I Maximal treadmill exercise

	Heart rate (cycles/min) maximal	Heart rate (cycles/min) increment from stage II onset to termination
Normal volunteers		
Control mean	188	+80
Range	174 201	65 102
+ Propranolol mean	155	+58
Range	147 180	41 65
% Decrease * mean	17	26
Range	10 21	9 42
Affected family members		
Control IV 6 II 1 IV 3	175 170 188	+76 77 97
+ Propranolol IV 6 II 1 IV 3	125 110 125	+37 26 35
% Decrease	29 35 34	51 66 64

Control Propranolol/Control

above maneuvers including maximal treadmill exercise were repeated In these studies electrocardiographic Leads I aV_F and V_5 were simultaneously recorded on an Avionics Model 3000 Exerstress Monitor at paper speeds of 25 and 50 mm/second

The two symptomatic family members II 1 and IV 6 had additional studies Trimethaphan camsylate was infused in the supine position sufficient to result in cuff blood pressures of 70 mm systolic in order to determine heart rate and Q T interval responses Left ventricular systolic time intervals were obtained in the control state and after combined beta adrenergic and parasympathetic blockade these results were compared to those of normal volunteers previously studied in our laboratory

The lower limit of normal for intrinsic heart rates (the heart rate observed after administration of atropine and propranolol) based upon age were determined according to the regression equations of Jose and associates

Results

Each of the affected family members responded to carotid sinus stimulation (minimum sinus cycle length prolongation of 17 per cent) without induction of abnormal (> 2 seconds) atrial or ventricular pauses, since carotid sinus stimulation was a gross maneuver no quantitative comparisons were attempted

Vagal withdrawal during sustained handgrip was assessed by comparing the mean value for the first three cycle lengths immediately following onset to the three cycle lengths immediately prior to the institution of isometric exercise The results are shown in Fig 3 left hand panel Each subject showed the expected decrease in cycle length which was abolished by atropine but not by propranolol The parasympathetically induced bradycardic response to Valsalva release is shown in Fig 3 right hand panel Again each subject showed an appropriate response abolished by atropine but not by propranolol

During sustained handgrip in the normal volunteers the decrement in sinus cycle length from ½ to 3 minutes averaged 8 per cent (range 2 to 16 per cent) the decrease was abolished in each subject after propranolol administration In the control state the decrement was 9 per cent 9 per cent and 12 per cent for II 1 IV 6 and IV 3 respectively and was similarly abolished by beta adrenergic blockade

In the control state each subject reached at least 90 per cent of their predicted maximal heart rate during treadmill exercise (Table I) The

hereditary Q T interval prolongation a disorder in which autonomic dysfunction might play a primary role Schwartz and colleagues[11] have recently called attention to multiple reports of low resting heart rates in affected individuals and to failure of exercise to increase heart rate in six of twelve subjects where such studies were performed The responses to partially blocking doses of atropine have been reported in three individuals one of whom failed to increase his heart rate [1, 20] These findings are of interest since Q T interval and T wave changes analogous to those found in the hereditary Q T interval prolongation syndromes have been produced in experimental animals by right stellate ganglionic section and left stellate ganglionic stimulation [1, 1] The heart rate responses described above are compatible with decreased sympathetic stimulation presumably through the right stellate ganglion which in dog experiments by Randall and Rohse[21] has been shown to be the primary effector of chronotropic actions

In the family forming the basis of the current report isotonic and isometric exercise yielded no appreciable abnormalities of heart rate responses in the control state However similar to the report of Pernot and associates[7] the two symptomatic family members evidenced abnormally depressed heart rate increments in response to atropine administration This could not solely be attributed to a defect in resting sympathetic stimulation as the response was depressed both with and without prior beta adrenergic blockade A high degree of resting vagal withdrawal is unlikely in view of resting heart rates in or near the bradycardic range and the ability to demonstrate such withdrawal during sustained hand grip Hypersensitivity to vagal stimuli as may be encountered in sick sinus syndrome[2] is also unlikely considering the normal responses to carotid sinus pressure and Valsalva release and the use of atropine dosages sufficient to insure complete parasympathetic blockade [3] A defect in sinus node automaticity tended to be excluded by their response to isoproterenol infusion [14]

The abnormally low increments with atropine in the sympathetic family members appear to be related to a depressed intrinsic heart rate This term has been coined by Jose and co workers[22, 23] and refers to the resting heart rate found after presumably complete pharmacologic autonomic blockade In II 1 and IV 6 abnormally low heart

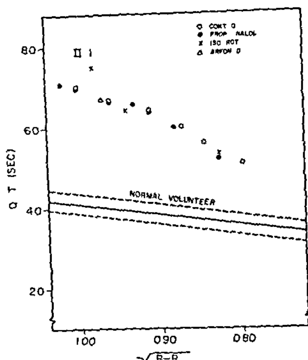


Fig 6 Q T intervals in affected family member II 1 The square root of the cycle length in seconds is shown on the abscissa and the observed Q T interval on the ordinate Control and propranolol values were obtained during the recovery from treadmill exercise Similar control values for the normal volunteers are indicated by the solid regression line the dashed lines represent two standard deviations. Except for a single isoproterenol value II 1 s Q T intervals were not significantly altered by autonomically active drugs *Isoprot* = isoproterenol

rates were found after administration of propranolol plus atropine and after ganglionic blockade with trimethaphan Jose and colleagues[19, 23, 24, 26] found the intrinsic heart rate to be directly related to myocardial contractility and inversely related to age The low rates observed in our patients were not apparently explicable on either basis The ability to increase intrinsic heart rate would be reflected in the response to maximal treadmill exercise following beta adrenergic blockade the normal volunteer data suggest parasympathetic influences are relatively unimportant in determining maximal heart rate responses during isotonic exercise The low maximal heart rate and subnormal increments in all three affected family members suggest an impaired ability to increase intrinsic heart rate

Though a low resting intrinsic heart rate was seen only in the symptomatic subjects its genesis and its relationship to symptomatic manifestations are obscure It may be related to intrinsic

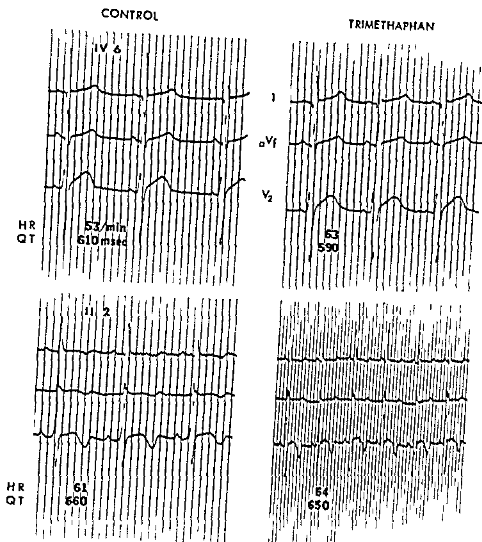


Fig 5 Heart rate and Q T interval responses to trimethaphan a ganglionic blocking agent in the symptomatic family members IV 6 20 years old and II 2 68 years old The findings illustrated during trimethaphan infusion were obtained when the blood pressure had decreased to 70 mm systolic Control blood pressures in IV 6 and II 2 were 120/64 and 130/92 respectively In both subjects the heart rate increment is abnormally decreased and the Q T interval is not altered apart from the change ascribable to the change in cycle length Time lines = 100 msec

ratory, the mean heart rate during trimethaphan infusion was 98/minute (range 73 to 116)

The isoproterenol infusion rate required to increase the resting heart rate by 30 cycles/ minute averaged 25 8 ng /Kg /minute (range 11 2 to 37 0) in the normal volunteers These values were not appreciably abnormal for II 1 (26 6 ng / Kg /minute) IV 6 (17 6), and IV 3 (18 2)

The durations of all measurable Q T intervals in the affected family members were prolonged However, as compared to the normal volunteers their intervals tended to decrease at a faster rate with decreasing cycle length Fig 6 shows the Q T intervals plotted against cycle length for subject II 1 The lower line is the regression of Q T interval on cycle length for the normal volunteers during recovery from treadmill exercise it was not significantly affected by propranolol The regression was also unchanged by propranolol in the affected family members Similar to subject IV 6 II 1s Q T interval was not significantly altered by trimethaphan apart from the change ascribable to the decrease in cycle length However, with the lowest rate of isoproterenol infusion II 1s Q T interval prolonged with a tendency toward alternation in T or U wave amplitude despite an increase in heart rate (Fig 7) As the isoproterenol infusion rate was augmented these changes disappeared, subsequent Q T intervals were not significantly different from the control state

Discussion

Autonomic influences on heart rate control in man have been extensively investigated but little information is available on such influences in

of local anesthetic has been reported to produce shortening lengthening[13] and no change[9] in Q T interval Since this procedure is performed blindly it may not result in blockade restricted to the ipsilateral stellate ganglion However surgical stellate ganglionectomy under direct vision in two individuals[5] has resulted in only transient Q T interval shortening Despite subsequent lengthening of the interval in these subjects there was protracted amelioration of symptoms and presumably a decrease in the incidence of ventricular arrhythmias leading to syncope Reduction in arrhythmia frequency may also constitute a non specific effect since in experimental animals left stellate ablation has been shown to increase ventricular fibrillation threshold[31] However these findings suggest that even if the effects of alterations in sympathetic tonus are non specific further investigation of their role in hereditary Q T interval prolongation is warranted by their potential for indicating beneficial modifications of the therapeutic regimen

Observations in a single family with hereditary Q T interval prolongation obviously cannot be made the basis for broad generalizations concerning the disease itself Our results only suggest some manifestations may have an intrinsic cardiac basis In that regard sinus bradycardia and probably abnormal heart rate responses to exercise cannot be invoked to support an extrinsic autonomic etiology unless an intrinsic defect is specifically excluded

Summary

Since extrinsic autonomic defects have been postulated to be a primary etiologic mechanism in hereditary Q T interval prolongation heart rate and Q T interval responses of three affected members of a family with Romano Ward syndrome and eight normal volunteers were studied in the control state and after blocking doses of propranolol atropine propranolol plus atropine and trimethaphan a ganglionic blocking agent The isoproterenol infusion rate required to increase resting heart rate by 30 per minute was determined During the control state cycle length changes in the normal volunteers and affected family members were not appreciably different with respect to prolongation during carotid sinus pressure and post Valsalva and shortening during the initial phase of hand grip These changes were abolished by atropine but not by propranolol As compared to the normal volunteers the affected family members maximal heart rates during treadmill exercise were similar but after propranolol they were significantly lower Isoproterenol sensitivity in affected family members was not significantly different from that in normal volunteers

The affected family members tended to have low resting heart rates and manifested abnormally low increments in rate with atropine Their heart rates were abnormally low after propranolol plus atropine and trimethaphan without evidence of depressed left ventricular function When changes in cycle length were accounted for affected family members Q T intervals during the control maneuvers were unaltered by propranolol trimethaphan and isoproterenol However one affected family member demonstrated disproportionate Q T interval lengthening and alternation in T or U wave amplitude with the lowest isoproterenol infusion rate these changes disappeared as the infusion rate was increased The present study suggests intrinsic cardiac changes are present in this family with Romano Ward syndrome Their relationship to any extrinsic sympathetic defect is unclear

The authors wish to thank Albert Treger M D for permission to study the family Miss Mary Ann Scully for technical assistance and Mrs. Minnie Flansbaum for secretarial assistance

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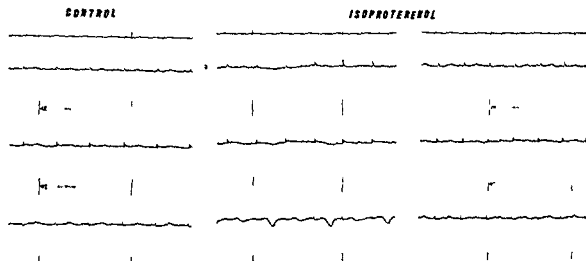


Fig 7 Electrocardiograms in subject II 1 during the control state (*first panel*) the lowest rate of isoproterenol infusion (*second panel*) and a higher infusion rate (*third panel*) During the control state the Q T interval is 0 65 sec At the lowest isoproterenol infusion rate the Q T interval prolongs to 0 74 sec despite an increase in heart rate and the T wave alternates in amplitude from cycle to cycle These changes disappear as the isoproterenol infusion rate is increased

sinus node disease as described by Fraser and co workers[3] and by James in three affected members of a family with Jervell Lange Nielsen syndrome In these subjects postmortem examination revealed medial thickening of the intra nodal portion of the sinus node artery extensive hemorrhage of the nodal-right atrial junction and hemorrhagic or degenerating parasympathetic ganglia near the node If the etiologic abnormality is indeed anatomic, it is difficult to conceive how it would bear a cause-effect relationship with Q T prolongation except at a metabolic or cellular level In the other few affected individuals where postmortem examination has been performed [1,8,9,8] the sinus node was examined in two instances[8,9] and no histologic abnormalities were found It is also significant that the atropine heart rate response was apparently abnormal in only one of the three previously reported instances The heart rate abnormalities although intrinsic appear to be concomitantly rather than causally related to Q T interval prolongation

In contrast to the observations of other authors [7,8,10,11] no Q T interval lengthening either absolute or relative to cycle length was observed following exercise of the affected family members The Q T interval tended to appropriately decrease with decreasing cycle length similar to the response in an affected individual observed by Roy and associates[10] where non adrenergically mediated increases in heart rate were produced by atrial pacing Since Q T interval tended to decrease at a more rapid rate than normal, it was evident that the patient had to be used as his own control to evaluate interval changes associated with concordant alterations in cycle length Correction of observed Q T intervals by the usual formula ($Q\ T/\sqrt{R-R}$) could have resulted in apparent shortening by any maneuver which increased heart rate We did not perform atrial pacing but observed no change in the regression of Q T interval on heart rate following β adrenergic blockade The interval was also not independently affected by blockade at the ganglionic level These findings suggest an intrinsic cardiac abnormality but do not exclude an additional significant extrinsic autonomic defect In one of our subjects disproportionate Q T interval lengthening and T wave alternans developed only at a relatively low isoproterenol infusion rate these findings disappeared as the sympathomimetic infusion rate was increased Thus the precise level of sympathetic stimulation may be of great importance in determining maximal Q T interval prolongation and perhaps maximal risk of sustained ventricular arrhythmias

While it is clear that changes in sympathetic tonus may result in significant symptomatic and/or electrocardiographic alterations in affected individuals the effects have not been uniform from patient to patient and it is uncertain whether these effects are specifically or non specifically related to the fundamental disorder producing Q T interval prolongation In affected individuals percutaneous left cervical infiltration

of local anesthetic has been reported to produce shortening lengthening[13] and no change in Q T interval Since this procedure is performed blindly it may not result in blockade restricted to the ipsilateral stellate ganglion However surgical stellate ganglionectomy under direct vision in two individuals[1, 13] has resulted in only transient Q T interval shortening Despite subsequent lengthening of the interval in these subjects there was protracted amelioration of symptoms and presumably a decrease in the incidence of ventricular arrhythmias leading to syncope Reduction in arrhythmia frequency may also constitute a non specific effect since in experimental animals left stellate ablation has been shown to increase ventricular fibrillation threshold[1, 2] However these findings suggest that even if the effects of alterations in sympathetic tonus are non specific further investigation of their role in hereditary Q T interval prolongation is warranted by their potential for indicating beneficial modifications of the therapeutic regimen

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Significance of new Q waves after bypass grafting Correlations between graft patency, ventriculogram and surgical venting technique

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New postoperative electrocardiographic Q waves have been described in eight to 40 per cent of patients undergoing bypass grafting for coronary artery disease[1] Various theories have been proposed to explain these new Q waves Correlations of new Q waves to vein bypass occlusion prolonged pump time or aortic cross clamping time are controversial[1-14] Indeed whether or not the appearance of new postoperative Q waves means real transmural myocardial infarction is not clear We report herein our experience with postoperative Q waves in 56 patients with vein bypass grafts and the relationship of new Q waves to ventricular venting graft patency and the postoperative ventriculogram Our observations indicate that (1) Not all Q waves are due to occlusion of the saphenous bypass grafts (as noted by others[1-16]) (2) A certain percentage of new Q waves may not reflect true transmural myocardial infarction especially when all the vein grafts are patent and the postoperative ventriculograms show improvement (3) Some new Q waves reflect true transmural infarction due to occlusion of grafts or of distal coronary arteries with deteriorated left ventriculograms (4) The high incidence of new Q waves in patients with ventricular vents is probably due to direct myocardial trauma at the apex of the left ventricle

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Material and methods

Between December 1970 and February 1976 720 patients underwent coronary bypass surgery at Long Island Jewish-Hillside Medical Center Forty nine patients were excluded because they also underwent partial ventricular resection prosthetic valve replacement or ventricular septal defect closure Of the remaining 671 patients 56 patients developed new Q waves making up the case material for the present study In 621 patients a saphenous vein graft was utilized for coronary bypass while in 50 patients the internal mammary artery was anastomosed to the left anterior descending artery

All patients had preoperative left and right heart catheterization and left ventricular and selective coronary angiography using the Judkins[6] or the Sones and Shirey[7] techniques In quantitating left ventricular dysfunction and the pattern of left ventricular contraction the same techniques and principles were used as previously reported[1] utilizing the descriptive terminology suggested by Herman and associates[3] Coronary arteries with at least 50 per cent reduction in diameter on coronary angiography were considered significantly stenosed and were bypassed whenever feasible The severity and the extent of coronary disease was graded according to the criteria of Bruschke and associates[2] Congestive

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Significance of new Q waves after bypass grafting Correlations between graft patency, ventriculogram and surgical venting technique

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New postoperative electrocardiographic Q waves have been described in eight to 40 per cent of patients undergoing bypass grafting for coronary artery disease[1-5] Various theories have been proposed to explain these new Q waves[6] Correlations of new Q waves to vein bypass occlusion prolonged pump time or aortic cross clamping time are controversial[1-4] Indeed whether or not the appearance of new postoperative Q waves means real transmural myocardial infarction is not clear We report herein our experience with postoperative Q waves in 56 patients with vein bypass grafts and the relationship of new Q waves to ventricular venting graft patency and the postoperative ventriculogram Our observations indicate that (1) Not all Q waves are due to occlusion of the saphenous bypass grafts (as noted by others[1]) (2) A certain percentage of new Q waves may not reflect true transmural myocardial infarction especially when all the vein grafts are patent and the postoperative ventriculograms show improvement (3) Some new Q waves reflect true transmural infarction due to occlusion of grafts or of distal coronary arteries with deteriorated left ventriculograms (4) The high incidence of new Q waves in patients with ventricular vents is probably due to direct myocardial trauma at the apex of the left ventricle

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Material and methods

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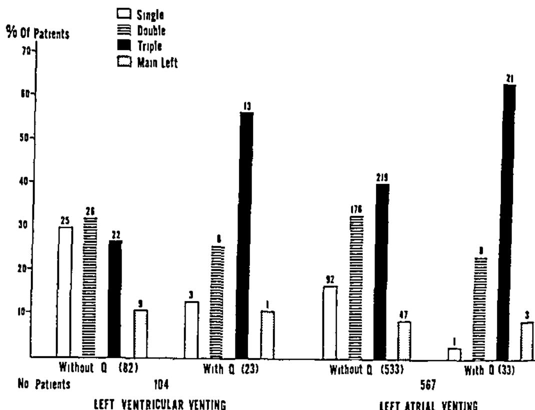


Fig 1 Comparison of the incidence of new Q waves in patients with ventricular or atrial venting revealed that patients with double or triple vessel disease had higher incidence of new Q waves as compared to those with single vessel disease

heart failure and cardiomegaly were defined according to the criteria we used in previous publication [22] Post bypass recatheterization and angiography were done 10 to 15 days after surgery in order to assess the patency of the grafts, and any change in left ventricular function Twelve lead electrocardiograms were performed on each patient on admission, on the day before surgery, then daily for the next four days and finally one day before discharge All angiograms and electro cardiograms were reviewed by two different cardiologists in the comparison of pre and post operative studies Electrocardiographic criteria used to evaluate the electrocardiogram were essentially Class I 1 and I 2 of the Minnesota code reported by Blackburn and associates [23] Cases presenting transient ST segment or T wave changes but without pathologic Q waves were not included in the infarction pattern group One hundred and forty two of the 671 patients were operated upon for preinfarction angina the same day of the cardiac catheterization as previously reported,[24] while 529 had elective surgery for angina

Patients with saphenous vein bypasses to all coronary arteries with luminal narrowing greater than 50 per cent were considered complete revascularizations while patients in whom saphenous vein bypasses could not be performed to one or more vessels with similar luminal narrowings were considered incomplete revascularizations

Operative technique

All patients had reversed saphenous vein aorto coronary bypass utilizing total cardiopulmonary support Priming solution was 5 per cent dextrose in one third normal saline Flow rates were 40 to 55 ml /Kg using a bubble oxygenerator with mean arterial pressures of at least 50 mm Hg In 104 patients the left ventricle was vented through the apex and in the remaining 567 patients the left ventricle was vented through the right superior pulmonary vein Moderate hypothermia was achieved by cooling the patient to 32° C After total cardiopulmonary bypass the ventricle was occasionally electrically defibrillated and intermittently clamped for the distal anastomo sis

Results

1 Effects of surgical venting technique in new Q wave incidence Of 671 operated on 104 (Group A) had intraoperative ventricular venting and 567 (Group B) had atrial venting The inci

dence of new Q waves in Group A was 23/104 (22 per cent) and in Group B 33/567 (5 8 per cent) ($p < 0.05$)

2 Relation of the clinical profile and underlying coronary disease to the incidence of new Q waves As seen in Table I comparison of age sex duration of angina coronary score history or location of prior myocardial infarction did not differ in patients with or without new Q waves Also there was no difference in the incidence of normal or abnormal left ventricular segmental wall motion between the groups Although there was a slightly higher incidence of cardiomegaly and congestive heart failure in patients who developed new Q waves the difference was not statistically significant Main left coronary stenosis or unstable angina pectoris did not affect the incidence of new Q waves Patients with double or triple vessel coronary disease had a higher incidence of new Q waves as compared to those with single vessel disease (Fig 1)

3 Relation of new Q waves to number of grafts placed In the entire series of 671 operated patients 56 (8 per cent) had new postoperative Q waves Of these 12 (6 per cent) occurred after single bypass in 207 patients 24 (8 per cent) after double bypass in 287 patients 18 (11 per cent) after triple bypass in 164 patients and two (15 per cent) after quadruple bypass in 13 patients Thirty one new Q waves appeared on the anterior and septal walls 23 on the inferior and infero lateral walls and two on lateral walls (Table II)

4 Relation of new Q waves to ungrafted vessels or to patent grafts with an occluded distal artery New Q waves appeared in the zone of myocardium supplied by grafted arteries in all except three patients with ventricular venting (Cases No 6 7 and 16) (Table III) In the latter three patients the Q waves occurred within zones of myocardium supplied by diseased but ungrafted vessels In all the patients with new Q waves who were restudied only two (Cases 37 and 40) (with atrial venting and deteriorated left ventriculograms) demonstrated patent grafts but an occluded coronary artery beyond the distal anastomotic site (Table IV)

5 Relation of new Q Waves to postoperative alteration of left ventricular function and graft closure In Group A (ventricular venting) 17 patients with new Q waves had postoperative ventriculograms Of these (Table III) three (18 per cent) had an improved ventriculogram and 0/7 graft closures 4 (24 per cent) had no change in the ventriculogram with 1/7 graft closure and in 10 patients (58 per cent) with deteriorated postoperative ventriculograms there were 7/16 graft closures (Table III) Of 17 patients in Group A who had postoperative ventriculograms five had single 11 had double and one had triple bypass grafts

In Group B (atrial venting) 25 patients with new Q waves were studied postoperatively Of these (Table IV) five (20 per cent) had an improved ventriculogram and 0/11 graft closures Fourteen (56 per cent) had an unchanged postoperative ventriculogram and 4/34 graft closures while six (24 per cent) had a deteriorated postoperative ventriculogram with 6/15 graft closures Of these 25 patients four had single eight had double 12 had triple and one had quadruple

Table I Clinical profile

	Without new Q waves		*With new Q waves*	
	No	%	No	%
Total number of patients	615		56	
Age (yrs)				
Mean	54 ± 6		53 ± 11	
Range	28-84		[illegible] 76	
Sex				
Male	506	82	49	87
Female	109	18	7	13
Unstable angina	13[illegible]	21	10	18
History of infarction	258	42	24	43
Documented ECG infarction				
Septal	16	9	2	7
Anterior	38		2	
Inferior	117	19	12	20
Inferior and anterior	21	3	3	5
Infero dorsal infero lateral and dorsal	12	[illegible]	3	5
Normal QRS	411	67	34	61
Enlarged heart	45	7	11	20
Congestive heart failure	25	4	5	9
Normal left ventricular contraction	230	37	24	43
Segmental hypokinesia of one wall	154	25	13	23
Akinesia of one wall	98	16	9	16
Akinesia or segmental hypokinesia of more than one wall	103	16	11	20
Generalized hypokinesia	3	0 5	0	0

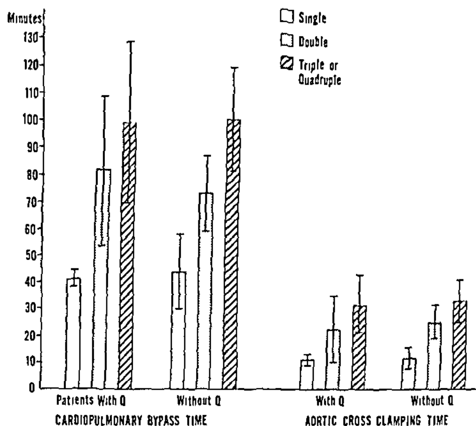


Fig 2 Comparison of over all cardiopulmonary bypass and aortic cross clamping time in patients with and without new Q waves did not show statistically significant difference

Table II Correlation of graft closure to the new Q waves and location of new Q waves in patients with ventricular and atrial venting

	Left ventricular venting		*Left atrial venting*		*Total*	
	No	*%*	*No*	*%*	*No*	*%*
Patients	23		33		56	
Grafts	42		80		122	
Pts studied	17	74	25	76	42	75
Grafts closed	8/30	27	9/60	15	17/90	19
New Q waves						
Anterior	12	52	12	36	24	43
Inferior	7	31	14	43	21	37
Infero lateral	2	9	0	0	2	4
Septal	1	4	6	18	7	12
Lateral	1	4	1	3	2	4

bypass grafts Although over all incidence of new Q waves was 22 per cent in patients with ventricular venting as compared to 5 8 per cent in those with atrial venting the graft closure rate in patients with new Q waves was 27 per cent in the ventricular vented group and 15 per cent in those with atrial venting

6 Relation of the location of new Q waves to complete versus incomplete revascularization and grafted vessels All the new Q waves occurred within the zone of myocardium supplied by a grafted artery except for 3/56 (5 per cent) of the patients These three new Q waves appeared in the inferior (Cases 6 and 7) or infero lateral (Case 16) wall in the group of patients with ventricular venting (Table III) Complete revascularization was performed in 50/104 (48 per cent) of the patients with ventricular venting in 369/567 (65 per cent) of those with atrial venting Patients with ventricular venting and new Q waves had 13/23 (57 per cent) complete revascularization and those with atrial venting 21/33 (64 per cent), the difference was statistically insignificant indicating that completeness of revascularization did not affect the incidence of new Q waves

7 Correlation of new Q waves to the duration of cardiopulmonary bypass aortic cross clamping time In 350 patients with atrial venting there were no significant differences in the over all duration of cardiopulmonary bypass or aortic cross clamping time in those with or without new Q waves whether they had single or multiple vessel coronary bypass surgery (Fig 2) In patients with new Q waves the incidence of prolonged cardiopulmonary bypass time exceeding 100 minutes for double (30 per cent) and 120

Table III Correlation of location of new Q wave patency of graft and postoperative ventriculogram in *Group A patients*

Patient	Grafts			Patency			Contraction		HX MI	Admission ECG Q wave	New Q
	LAD	RCA	CX	LAD	RCA	CX	Preop	Postop			
LVG improved											
1	X	X		+	+		As Ant	Normal	1	Inferior	Anterior
2	X	X		+	+		As Ant	Normal	1	RBBB + Lateral	Inferior
3	X	X	X	+	+	+	As Ant	Normal	1	Inferior (narrow Q)	Inferior (wide Q)
LVG unchanged											
4	X		X	+		0	Normal	Normal	0	Normal	Septal
	X			+			Normal	Normal	0	Inferior + Lateral	LAH + Anterior
6	X		X	+		+	Normal	Normal	0	Normal	Inferior
7	X		X	+		+	Normal	Normal	1	T aV	Inferior
LVG Deteriorated											
8	X	X		+	+		Ak Apic	Ak<Ant / Apic	3	T v	Anterior
9	X			0			Normal	Ak Apic	0	Normal	Anterior
10	X	X		0	0		As Apic	Ak<Ant / Apic	0	Inferior	Anterior
11	X	X		0	0		Normal	Ak Apic	2	T v	Anterior
12	X			0			As Ant	Ak Ant	0	LAH QRS WNL	Anterior
13	X	X		+	+		Ak Ant	As-Ant Ak Inf + Apic	3	Anterior	Inferior
14	X	X		+	+		As-Inf	Ak Inf	0	Normal	Inferior
15		X			+		Normal	Ak Apic	0	Normal	Inferior
16	X			0			Normal	Ak Apic	0	Normal	Inferior
17	X	X		+	+		As Inf	Ak<Inf / Apic	2	Normal	Inferolateral

Abbreviations LAD = left anterior descending coronary artery RCA = right coronary artery CX = circumflex coronary artery Ak = Akinesia As = Segmental hypokinesia

minutes for triple or multiple bypass grafts (33 per cent) as compared to those with no Q waves (18 per cent and 13 per cent respectively) were slightly higher

8 Disappearance of Q waves Two of our patients after coronary bypass surgery lost long standing anterior Q waves Postoperative angiography in these two patients revealed patent saphenous bypass grafts and improved left ventriculogram in one while in the other the left ventriculogram was unchanged

9 Relation of mortality to graft patency Twelve patients died within one month after bypass surgery (Table V) Three patients died in the operating room One of them (Case 2) probably had a myocardial infarction the morning of surgery Of nine patients who died within two weeks after surgery two died of non cardiac causes one died of combined cardiac and non cardiac causes whereas six patients deaths were secondary to myocardial infarction The mortality in two patients who died after discharge at home was due to myocardial infarction in one (Case 10) and in the other due to myocardial infarction or ventricular arrhythmia (Case 11) It should be mentioned that 2/12 (17 per cent) who died had balloon assist prior to surgery for persistent angina or cardiogenic shock (Cases 6 and 11) and one patient was brought to the operating room after arrest while external cardiac massage was being performed (Case 1) Of 12 patients who died three (25 per cent) had main left coronary stenosis

Discussion

An 8 per cent incidence of new Q waves in our series is lower than reported by others [1, 15, 23] Contrary to the report of Williams and asso

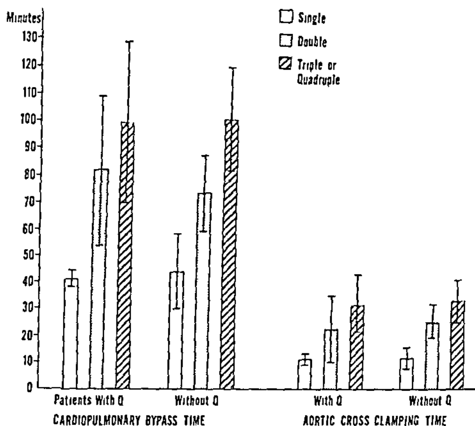


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mortality rate of only 6 per cent (3/50) (Cases 4 6 8 Table V) in the patients developing post bypass new Q waves was much lower than reported mortality rate in CCU s by different centers namely 9 8 per cent to 23 per cent [6,7] This suggests that new post bypass Q waves may not represent true transmural myocardial infarctions Most of the patients with sudden development of postoperative new Q waves had a benign hospital course and were not clinically different from patients without new Q waves This has also been noted by others [3, 15, 6] Patients with presumed true myocardial infarction not only had elevated SGOT and other enzyme levels but their electrocardiograms demonstrated evolutionary changes of transmural myocardial infarction usually localized on the anterior wall of the left ventricle Although Fruehan and associates[15] noted that 74 per cent (28/38) of new Q waves were located in the inferior dorsal or inferolateral wall in their series of 199 patients we encountered new Q waves in those locations in only 41 per cent (23/56)

Three of 56 patients with new Q waves and a history of previous myocardial infarction (Cases 3 20 36 Tables III and IV) developed significant Q waves in the inferior or anterior wall sites of previous narrow Q waves These electrocardiographic changes which suggest unmasking of an old myocardial infarction pattern may also be due to a localized conduction disturbance in an area of previous infarction due to redistribution of electrical forces after bypass surgery or to a change of axis secondary to surgery The left ventriculograms in these patients improved or did not change after the appearance of significant new Q waves However none of our patients after coronary bypass surgery manifested the phenomenon of unmasking of old infarction described by Bassan and associates It is worth mentioning that two of our patients after coronary bypass surgery and patent grafts lost long standing anterior Q waves which also has been observed by Conde and associates[3]

A striking decrease in the incidence of postoperative Q waves (from 22 per cent to 5 8 per cent) occurred when atrial rather than ventricular venting was adopted This result may be due in part to improved surgical bypass techniques since the ventricular vented cases were done at the start of the coronary bypass surgery program in our institution The over all incidence of saphenous bypass graft closure was higher in the early operated group In the ventricular venting group the graft closure rate was 22 per cent versus 8 per cent in those patients with atrial venting In patients with new Q waves and ventricular venting who had a postoperative study (Table II) the graft closure rate was twice as high as compared to the atrial venting group (27 per cent versus 15 per cent) However the incidence of the new Q waves was much higher in the ventricular venting group (22 per cent) as compared at atrial venting patients (58 per cent) Thus improved surgical techniques and fewer graft closures alone cannot explain such a drop in the incidence of new Q waves The clear implication is that sufficient myocardial trauma results from ventricular venting to result in pathologic Q waves The anatomic placement of ventricular vents at or near the apex could account for either inferior or anterior wall localization of the postoperative Q waves Since the ventricular trauma produced by venting is not due to arterial occlusion there is no wide surrounding ischemic area Thus it is not surprising that postoperative Q waves attributable to venting are not usually associated with impaired ventricular function in the absence of *graft occlusion Indeed* improved ventricular function may be observed However in four patients (Cases 13 14 15 and 17) in whom new inferior Q waves developed new dysfunction of the inferior wall and open grafts to the right coronary artery could be demonstrated Here we assume that the deterioration in the ventriculogram was probably secondary to the trauma of venting In contrast are Cases 7 9 10 11 12 16 19 38 and 39 all of whom developed new anterior Q waves and anterior wall dysfunction in the presence of occluded grafts to the left anterior descending artery or its diagonal branch Here the assumption must be that true infarction secondary to inadequate arterial and graft inflow occurred

The incidence of new Q waves was higher in patients with double triple or quadruple bypass surgery as compared to those with a single bypass as reported by others Although our patients with atrial venting had a higher percentage of complete revascularizations the incidence of new Q waves was not affected by complete or incomplete revascularization in patients in either the atrial or ventricular venting groups All of the new Q waves occurred within

Table IV Correlation of location of new Q wave patency of graft, and postoperative ventriculogram in Group B patients

Patient	Grafts LAD	Grafts RCA	Grafts CX	Patency LAD	Patency RCA	Patency CX	Contraction Preop	Contraction Postop	HX MI	Admission ECG Q wave	New Q
LVG improved											
18	X	X	X	+	+	+	As < Ant / Apic	Normal	0	T, ,	Septal
19	X†			+			As Apic	Normal	0	Normal	Septal
20	X	X		+	+		Ak < Apic / Inf	As < Apic / Inf	+1	Small Q with good R V V,	QS V V,
21	X	X		+	+		Ak < Ant / Apic	Normal	0	TV, V	Inferior
22	X	X	X	+	+	+	As < Ant / Inf	Normal	0	Normal	Inferior
LVG unchanged											
23	X	X	X	+	0	+	As Apic	As Apic	1	Normal	Septal
24	X		X	+		+	Ak Inf	Ak Inf	1	Inferior	Anterior
25	X†			+			As Ant	As Ant	2	Infero dorso lateral	Anterior
			X			0	Ak Inf	Ak Inf			
26	X	X	X	+	+	+	Ak Apic	Ak Apic	0	Normal	Anterior
27	X	X	X	+	+	0	Normal	Normal	0	Normal	Inferior
28	X	X		+	+		Normal	Normal	1	TV, V_6	Inferior
29	X	X	X	+	+	+	Normal	Normal	0	T, ,, aV_F	Inferior
30	X	X		+	+		Normal	Normal	0	Normal	Inferior
31	X	X	X	+	+	+	Normal	Normal	0	Normal	Inferior
32		X			0		Ak Inf	Ak Inf	0	T, ,	Inferior
33	X	X	X	+	+	+	Normal	Normal	0	Normal	Inferior
34	X	X	X	+	+	+	Normal	Normal	0	T, aV_F	Inferior
35	X†	X	X	+	+	0	Normal	Normal	1	Normal	Inferior
36		X	X		+	+	Normal	Normal	2	Anterior + small Q II III aV_F	Inferior
LVG deteriorated											
37	X			+*			Normal	Ak Apic	0	Normal	Septal
38	0		X	0		+	As Ant	Ak Ant	1	Q II III aV_F	Anterior
	X			+			Ak Basal	Ak Basal			
39	X	X	X	0	0	0	As Ant	Ak < Ant / Inf	1	Inferior + lateral	Anterior
40	X	X	X	+	+	+	Normal	Ak < Ant / Apic	0	Normal	Anterior
41	X		X	0		+	As < Ant / Apic	Ak Apic	0	T, ,	Lateral
42	X†	X	X	+	+	0	Normal	Ak Inf	0	T ,	Inferior

Abbreviations as in Table III
*Patent graft but occluded distal left anterior descending artery (cases 37 and 40)
†Internal mammary anastomosis to left anterior descending artery

ciates[1] main left coronary stenosis did not increase the incidence of new Q waves The age sex, duration of disease preinfarction angina previous myocardial infarction or abnormal left ventricular wall motion did not affect the incidence of new Q waves Patients with double or triple vessel disease as well as those with cardiomegaly or congestive heart failure had a higher incidence of new Q waves but this difference was not statistically significant Of 12 patients who died after coronary bypass surgery, eight died (Table V) of definite acute myocardial infarction one probably of acute myocardial infarction or ventricular tachyarrhythmia (Case 11 Table V) two of massive pulmonary embolism and one after an extensive cerebrovascular accident Of these 12 patients 25 per cent had significant main left coronary artery disease The

Comments
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The morning of surgery had protracted chest pain with ST elevation. Autopsy showed fresh anterior infarction
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Postoperative stormy course No autopsy
Autopsy showed pulmonary embolism with patent grafts
Balloon assist + nitroprusside for persistent angina Po top developed anterior Q wave then LBBB before death
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Developed LBBB + LPH before death
No autopsy
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Balloon assisted angiograms done Discharged home after triple patent grafts Died in his sleep
Protracted pleuritic pain Had persistent pericardial rub Autopsy showed bilateral massive pulmonary emboli + fresh anterior infarct and patent grafts

per cent of left ventriculograms deteriorated while 43 per cent were unchanged and 19 per cent improved after surgery Indeed in the patients without new Q waves 9 per cent (77/885) of grafts were closed indicating that graft occlusion can occur without necessarily causing electrocardiographic changes of transmural myocardial infarction It is important to note that in our series patients with single bypass grafts in whom the postoperative left ventriculogram showed deterioration invariably had an occluded bypass graft or a patent graft with occlusion of the coronary artery distal to the anastomosis (Tables III and IV) At least four or five patients developed severe hypotension prior to bypass surgery These patients most likely sustained myocardial infarction at that moment and electrocardiographic changes of transmural myocardial infarction appeared after completion of the bypass due to reperfusion of the infarcted area since bypass grafts studied postoperatively were patent in this group The delayed appearance of new Q waves after coronary occlusion in dogs has been explained by Blumenthal and associates[31] Possible preservation of the sarcolemmal membranes delays the appearance of Q waves in the early phase of infarction but after reperfusion disruption of these membranes accelerates the emergency of Q waves

When new Q waves appeared after bypass using the atrial venting technique with ventricular function unimproved or worsened graft closure or occlusion of the distal coronary artery was common A compromised arterial inflow and true myocardial infarction must be presumed

Of great interest are those patients with new Q waves following atrial venting with improved ventriculograms and patent grafts The new Q waves must be a consequence of surgical trauma since aortic cross clamp and cardiopulmonary bypass times were not significantly prolonged Two possibilities are suggested First direct myocardial damage with muscle necrosis may occur sufficient to produce Q waves but nevertheless undetectable by ventriculography Second the surgical trauma might result in localized ventricular conduction delays or blocks affecting the early QRS balance as postulated by Castellanos and Lemberg[32] They theorized that such local delays in ischemic tissue result in slurring or widening of the QRS producing 'infarct Qs It seems reasonable that a similar mechanism in traumatized tissue may account for postoperative Q waves in these patients with improved ventriculograms and patent grafts

Clinical significance and prognosis Post bypass grafting Q waves as described and discussed have a varied pathogenesis When accompanied by improvement in ventricular function and patent grafts they are of little significance and do not carry the prognostic importance of myocardial infarction as it occurs in the natural course of arteriosclerotic heart disease In contrast when accompanied by graft closure and deteriorated ventricular function the mechanism may be presumed ischemic and the prognosis must take into account the likelihood of permanent or long term localized ventricular dysfunction

Summary

New Q waves were observed in 56 (8 per cent) of 671 patients undergoing saphenous vein bypass

Table V Circumstances and causes of death

Patient no	No of diseased vessels	Old myocardial infarction	Died			New Q waves	Causes of death		
			In OR	Within 2 wks	Within 1 month		Infarction	Pulmonary embolism	Cerebro-vascular accide
LV VENT									
1	3	Inferior	–	+	–	Anterior	+	–	–
2	M 3	Inferior	+	–	–	–	+	–	–
3	2	Inferior	–	+	–	–	–	–	+
LA VENT									
4	3	0	–	+	–	Inferior + LPH + RBBB	+	–	–
5	2	Anterior + LAH	–	+	–	–	–	+	–
6	3	Inferior	–	+	–	Anterior	+	–	–
7	3	0	+	–	–	–	+	–	–
8	3	Anterior + Inferior	–	+	–	Anterior	+	–	–
9	M 2	0	+	–	–	–	+	–	–
10	1	0	–	–	+	Anterior (3 wks postop)	+	–	–
11	3	Anterior + inferior	–	–	+	–	Probable	–	–
12	M 3	0	–	+	–	–	+	+	–

Abbreviations M = main left coronary artery LAH = left anterior hemiblock LPH = left posterior hemiblock RBBB = right bundle branch block

the zone of myocardium supplied by the grafted artery except three (5 per cent) of the patients in the ventricular vented group in whom the new Q wave appeared in non grafted vessel zones of inferior or infero lateral wall This result is different from the report of Assad Morell and colleagues [11] in which 25 per cent of the patients manifested new Q waves in a zone of myocardium supplied by a diseased ungrafted artery It is worth mentioning that in three patients with atrial venting and with patent saphenous vein bypass grafts the coronary artery distal to the anastomosis was closed This explains the appearance of their new Q waves as well as the observed deterioration of left ventricular contractility

Although Anderson and associates[3] noted no direct correlation between ECG evidence of transmural myocardial infarction and graft closure they did not comment on the corresponding ventriculography Brewer and associates[16] confirmed these findings in autopsy studies of patients dying after coronary bypass surgery In the present study new Q waves were noted in patients with deteriorated, unchanged or even improved ventriculograms When the data on new Q waves and postoperative ventricular function were correlated no direct relationship could be seen However, when graft patency was also considered, a clear relationship emerged Improved postoperative ventricular function correlated well with graft patency, despite Q waves Unimproved or deteriorated ventricular function did not predict graft occlusion since more than half of the vein grafts placed in these patients were patent Assad Morell and associates[11] also noted a lack of correlation between graft closure and electrocardiographic and angiographic evidence of myocardial infarction Half their 32 patients had patent grafts despite evidence of myocardial infarction in the area of distribution of the grafted vessels

In our series only 19 per cent of grafts were closed in patients with new Q waves and only 38

Comments

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per cent of left ventriculograms deteriorated while 43 per cent were unchanged and 19 per cent improved after surgery. Indeed, in the patients without new Q waves, 9 per cent (77/885) of grafts were closed, indicating that graft occlusion can occur without necessarily causing electrocardiographic changes of transmural myocardial infarction. It is important to note that in our series patients with single bypass grafts in whom the postoperative left ventriculogram showed deterioration invariably had an occluded bypass graft or a patent graft with occlusion of the coronary artery distal to the anastomosis (Tables III and IV). At least four or five patients developed severe hypotension prior to bypass surgery. These patients most likely sustained myocardial infarction at that moment and electrocardiographic changes of transmural myocardial infarction appeared after completion of the bypass due to reperfusion of the infarcted area, since bypass grafts studied postoperatively were patent in this group. The delayed appearance of new Q waves after coronary occlusion in dogs has been explained by Blumenthal and associates.[31] Possible preservation of the sarcolemmal membranes delays the appearance of Q waves in the early phase of infarction, but after reperfusion, disruption of these membranes accelerates the emergency of Q waves.

When new Q waves appeared after bypass using the atrial venting technique with ventricular function unimproved or worsened, graft closure or occlusion of the distal coronary artery was common. A compromised arterial inflow and true myocardial infarction must be presumed.

Of great interest are those patients with new Q waves following atrial venting with improved ventriculograms and patent grafts. The new Q waves must be a consequence of surgical trauma since aortic cross clamp and cardiopulmonary bypass times were not significantly prolonged. Two possibilities are suggested. First, direct myocardial damage with muscle necrosis may occur sufficient to produce Q waves but nevertheless undetectable by ventriculography. Second, the surgical trauma might result in localized ventricular conduction delays or blocks affecting the early QRS balance, as postulated by Castellanos and Lemberg.[32] They theorized that such local delays in ischemic tissue result in slurring or widening of the QRS, producing infarct Qs. It seems reasonable that a similar mechanism in traumatized tissue may account for postoperative Q waves in these patients with improved ventriculograms and patent grafts.

Clinical significance and prognosis. Post bypass grafting Q waves as described and discussed have a varied pathogenesis. When accompanied by improvement in ventricular function and patent grafts, they are of little significance and do not carry the prognostic importance of myocardial infarction as it occurs in the natural course of arteriosclerotic heart disease. In contrast, when accompanied by graft closure and deteriorated ventricular function, the mechanism may be presumed ischemic and the prognosis must take into account the likelihood of permanent or long term localized ventricular dysfunction.

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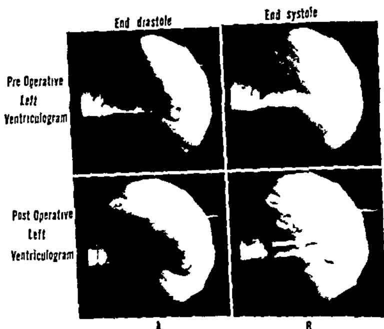


Fig 5 Pre and postoperative left ventriculograms of a patient with atrial venting and new anterior Q waves (Case No 37) Postoperatively the vein graft was patent with occluded distal left anterior descending artery and new hypokinesia of the apical segment of the left ventricle (*arrow*)

of angina previous myocardial infarction or main left coronary lesions did not affect the incidence of new Q waves Although new Q waves were more frequent in patients with preoperative cardiomegaly and congestive heart failure this difference was not statistically significant However there was no significant difference in the over all cardiopulmonary bypass or aortic cross clamping time in patients with or without new Q waves Cardiopulmonary bypass time exceeding 100 minutes in patients with double bypasses and more than 120 minutes with multiple bypasses were more frequent in patients with new Q waves Completeness or incompleteness of the revascularization procedure did not affect the incidence of new Q waves In all but three patients with ventricular venting new Q waves appeared in a zone of myocardium supplied by a grafted artery In the three exceptions the Q waves occurred within the zone of myocardium supplied by diseased but ungrafted vessels In the ventricular vented group 7 (41 per cent) demonstrated an improved or unchanged postoperative ventriculogram with 7 per cent graft closure and 10 (59 per cent) had deteriorated ventriculograms with 44 per cent graft closure In 25 patients with atrial venting 19 (76 per cent) showed improved or unchanged postoperative ventriculogram with 12 percent graft closure and 6 (14 per cent) had deteriorated ventriculograms with 40 per cent graft closure Although over all incidence of new Q waves was 22 per cent in patients with ventricular venting as compared to 5 8 per cent in those with atrial venting the graft closure rate in patients with new Q waves was 27 per cent in ventricular vented group and 15 per cent in those with atrial venting

These findings indicate a poor correlation between new Q waves and graft closure Improved postoperative ventriculograms correlated well with graft patency despite new Q waves The etiology of new post bypass graft Q waves are varied They include direct ventricular trauma and conduction delays resulting from surgery or venting as well as true ischemic infarction Infarction may be due to compromised arterial inflow either in non operated diseased vessels in vessels distal to anastomoses with patent grafts or due to graft closure

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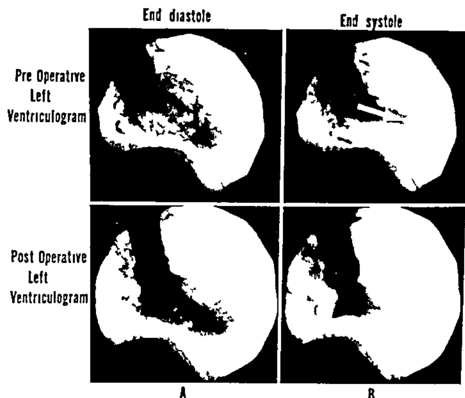


Fig 3 Pre and postoperative angiographic study of a patient with atrial venting who after triple vein bypass surgery developed new septal Q waves (Case No 18) As seen here segmental hypokinesia of the anteroapical segment of the left ventricle (*arrow*) was no more present in the postoperative left ventriculogram

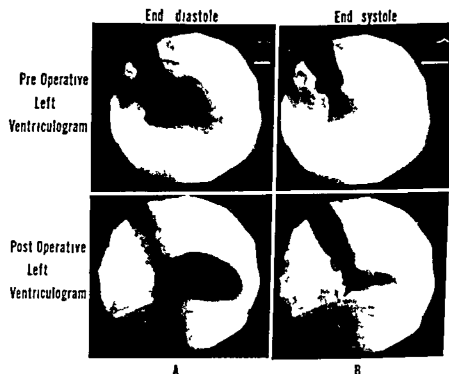


Fig 4 Comparison of pre and postoperative left ventricular contractile pattern of Case No 27 Left ventriculogram did not show any significant change although postop he developed new inferior Q waves

grafting with an over all mortality rate of 1 8 per cent Forty two of the 56 (75 per cent) had postoperative ventriculograms and arteriograms and are reported herein Ventricular venting was used intraoperatively in 17 patients and atrial venting in 25 Thirty one patients had new anterior and/or septal Q waves while 23 had inferior or infero lateral and 2 had lateral Q waves The incidence of new Q waves in patients with ventricular venting was 22 per cent and in those with atrial venting it was 5 8 per cent ($p < 0.05$) Age sex duration of disease severity

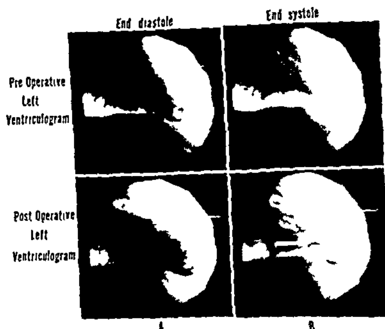


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'Silent' myocardial ischemia during and after exercise testing in patients with coronary artery disease*

H Eugene Lindsey Jr M D
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During exercise testing subjective symptoms of chest pain can often be related to objective evidence of myocardial ischemia when ST segment depression or elevation appears on the ECG[1] Frequently however individuals with coronary artery disease have ischemic ECG responses to exercise testing without experiencing angina or its equivalents[2-4] indicating that there may be silent or asymptomatic myocardial ischemia just as there may be silent myocardial infarction[5] Because the clinical and angiographical features of asymptomatic and symptomatic myocardial ischemia have not been compared in detail in previous exercise studies we studied the subjective as well as the objective responses to exercise testing in a group of patients with exercise induced ischemic ST changes in whom coronary artery disease was demonstrated by angiography

Methods

Patient selection In evaluating the phenomenon of silent myocardial ischemia we studied the exercise responses of 232 consecutive patients (tested between 1972 and 74) with chest pain syndromes who were free of concomitant valvular pericardial or congenital heart disease One hundred eighty four patients had angiographically determined coronary artery disease and 48 had normal coronary arteriograms Because of the difficulty in relating the presence or absence of chest pain to myocardial ischemia during a *negative* exercise test we were most interested in the patient who had an abnormal or *positive* exercise test As expected from prior studies[6] only about 20 per cent of the patients with normal coronary arteriograms had a positive exercise test a number (11) too small for meaningful analysis Therefore the present report concerns only the subgroup of 122 consecutive patients with coronary artery disease and an abnormal ECG response to exercise testing These 122 consecutive patients all had clinically stable coronary artery disease (defined for this study as > 75 per cent stenosis in the diameter of one or more of the three coronary arteries or their major branches) and neither left bundle branch block nor other disorders which might affect interpretation of the post exercise ECG[7] such as alcoholism thyroid disease valvular or pericardial heart disease or electrolyte abnormalities Patients were queried (and their medical records examined) to determine whether they had a history of typical angina pectoris or a prior myocardial infarction or manifested signs of clinical congestive heart failure hypertension (blood pressure > 140/90 at any time) or hyperglycemia (fasting or two hour postprandial blood sugar > 120 mg per cent) or were taking a digitalis preparation or propranolol Patients who were on propranolol had their medication held for 24 to 36 hours prior to exercise testing

Exercise testing Each patient was evaluated by one or more exercise tests on the day prior to angiography The exercise protocol consisted of a double two step test for which the end point was chest pain (or its usual equivalent in each

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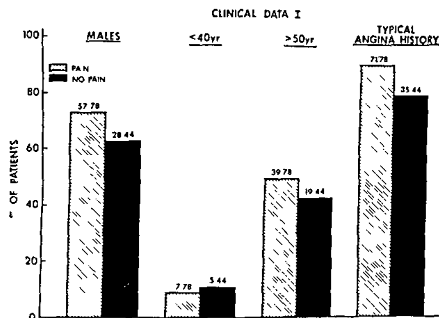


Fig 1 Sex distribution age and history of typical angina in patients with and without angina during or after exercise testing

patient) or completion of the test Standard 12 lead ECGs were recorded with patients in the supine position before immediately after and three five and eight minutes after the test A two step test was considered positive if there was new or additional J point depression $\geq$ 0 5 mm with a flat or depressed ST segment in any lead for at least 80 milliseconds immediately after and up to 8 minutes post exercise [1] If the test was negative or equivocal a bicycle ergometer test was performed after a 30 to 60 minute rest period Patients were exercised with a bicycle ergometer at an initial work load of 300 k p m and this load was increased every three minutes by 150 k p m until 85 per cent of the maximum predicted heart rate was reached or symptoms forced the patient to stop Lead V_5 was monitored during the exercise test and recorded at minute intervals, and the standard 12 lead ECG was recorded at the same time intervals as the two step test A bicycle test was considered positive if the ST segment depression was $\geq$ 1 0 mm during or up to 8 minutes post exercise [1] During and after the test patients were queried as to the presence of chest arm or jaw pain, pressure tightness or discomfort as well as fatigue or dyspnea

Coronary angiography Coronary angiograms were recorded on 16 mm cine film in multiple projections using the Sones or Judkins technique They were interpreted by consensus of two or more members of the senior cardiology staff usually without prior knowledge of whether the exercise test resulted in pain or not

Left ventriculography Left ventriculograms were obtained in the right anterior oblique projection using multi holed catheters and power injections of 40 to 50 ml of 76 per cent meglumine sodium diazitroate Volumes and ejection fractions were calculated by standard area-length methods utilized in our laboratory and reported in detail previously [8]

Results

Frequency of angina in patients with positive exercise tests Seventy eight of the 122 patients with positive exercise tests experienced angina or its usual equivalents Forty four patients had no such symptoms but 12 of these 44 pain free patients had other symptoms which forced them to stop their tests Three stopped because of shortness of breath and nine stopped because of generalized fatigue The remaining 32 patients stopped only because they had completed the two step test or achieved 85 per cent of their predicted heart rate on the bicycle test

Comparison of subgroups with and without angina

1 Age and sex distribution (Fig 1) Seventy three per cent of the patients with pain were males compared to 64 per cent of the patients without pain (pNS) Mean age in the patients with pain was 49 ± 4 (S E M) years and 47 ± 3 years in the non pain group (pNS) * The percent

* Statistical significance determined by t test all other comparisons were by chi square tests

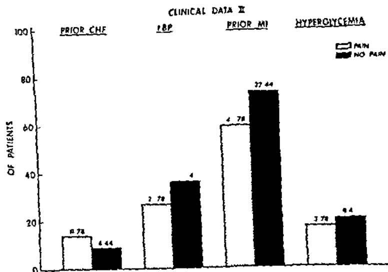


Fig 2 Frequency of congestive heart failure (*CHF*) hypertension (↑*BP*) myocardial infarction (*MI*) and hyperglycemia in the two subgroups of patient

ages of patients in the < 40 and > 50 age groups were also similar

2 *Prior history of typical angina (Fig 1)* When the two subgroups were compared there was no statistically significant difference (91 per cent vs 80 per cent) in the frequency of a history of typical angina pectoris (exertion related chest discomfort promptly relieved by rest and/or nitroglycerin) Further analysis of the pain patterns indicated that there were similar numbers of NYHA Class III and Class IV patients in each subgroup

3 *Clinical congestive heart failure (Fig 2)* In each subgroup there were statistically similar numbers of patients with overt clinical congestive heart failure (14 per cent vs 9 per cent)

4 *Hypertension (Fig 2)* There were similar percentages of patients in each group with blood pressure higher than 140/90 mm Hg or a prior history of treated hypertension (27 per cent vs 36 per cent)

5 *Prior history of myocardial infarction (Fig 2)* Prior transmural or non transmural myocardial infarction (by history of ECG and/or cardiac enzyme evolution) was a common finding in this study but the frequency was statistically similar in each group of patients (59 per cent vs 73 per cent)

6 *Hyperglycemia (Fig 2)* The frequency of hyperglycemia and/or treated diabetes mellitus was similar in each group (17 per cent vs 20 per cent)

7 *Drug therapy (Fig 3)* Relatively small but almost equal numbers of patients were taking digitalis preparations prior to the study (18 per cent vs 16 per cent) As noted earlier propranolol was held for 24 to 36 hours prior to the exercise test and angiography Forty seven per cent of the patients with pain were taking this drug compared to 36 per cent of the pain free group (pNS)

8 *Resting ECG (Fig 4)* The frequency of normal control ECGs ECGs with minor ST T abnormalities and ECGs diagnostic of prior transmural myocardial infarction were almost identical in the group with chest pain on exercise testing compared to the group without pain

9 *Angiographic findings (Fig 5)* Multivessel disease was a frequent finding in these patients (83 per cent vs 75 per cent pNS) as was the frequency of collateral vessels (62 per cent vs 70 per cent pNS) Impaired left ventricular function (defined as an ejection fraction less than 50)[9] was less common but was found with nearly equal frequency in both subgroups (24 per cent vs 30 per cent pNS)

10 *Exercise tests (Fig 6)* Exercise tests were analyzed to determine the maximum heart rate and the extent of the ischemic response There were nearly equal numbers of patients in each group who had heart rates greater than 120 recorded during or immediately after exercise (50 per cent vs 43 per cent) suggesting equivalent degrees of stress The frequency of strongly posi

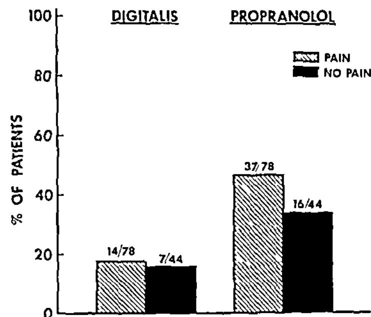


Fig 3 Use of digitalis and propranolol by the patients in the study

tive exercise tests (greater than 2 mm ST segment depression in any lead) was 42 per cent vs 41 per cent In addition the lead location of the most positive response was also similar in both groups as was the post exercise time interval in which the maximum ST depression developed Finally, the numbers of patients tested by only the double two step test versus those with additional bicycle ergometry was similar in each group with 64 per cent of the patients with pain having only a double two step test compared to 70 per cent of the pain free group

In addition to the above analyses, various combinations such as hypertension *and* hypergly cemia were also compared with no significant differences noted between the two groups

Discussion

The present report concerns a group of 122 patients with coronary artery disease and an abnormal ECG response to exercise testing and examines their subjective response to presumed myocardial ischemia In this study clinical and angiographic findings in the 78 patients with anginal pain or its equivalents during or after a positive exercise test were compared to the 44 patients without such symptoms The two sub groups in the present study were shown to be similar statistically in selected aspects of their clinical histories resting ECGs technical aspects of exercise testing exercise test results extent of disease by angiography, and left ventricular func tion A majority of the patients in both groups had a history of angina that could be described as typical, but this occurred as frequently and with the same severity in both subgroups Similarly patients with myocardial infarction by history and by resting ECG were found with similar frequency in both groups and the group without chest pain was not comprised primarily of those patients whose marker for coronary artery disease had been a myocardial infarction rather than angina Since diabetes mellitus and hypertension have a higher than expected incidence in patients with clinically unrecognized myocardial infarc tion[5] one might ascribe differences in the frequency of pain free exercise tests to differences in the numbers of the hyperglycemic and hyper tensive patients in the two groups, but no such differences were found The resting ECGs were also examined in the two groups Although the presence of prior ST T abnormalities might be expected to cause some difficulties in interpreting post exercise changes and possibly result in false positive (as well as false negative) results patients with ST T abnormalities were equally distributed between the two groups Drug therapy might also contribute to problems in interpreting ECG changes as well as modifying the subjective response to ischemia yet similar numbers of patients in each group had been on propranolol or digitalis preparations prior to hospitalization and propranolol was routinely held in this group of clinically stable patients for 24 to 36 hours prior to exercise studies Analysis of the exercise test results shows that patients with pain did not have more strongly ischemic responses than patients without pain nor did the latter group have a reduced prevalence of lower exercise or post exercise heart rates, which would have suggested a less stressful test The lead location of the most positive response was similar in both groups Also there were similar numbers of patients in each group tested by both bicycle ergometry and two step tests so that the mech anisms of testing should not have affected the results The frequencies of multivessel disease and collateral circulation were the same in both groups and impaired ventricular function (de creased ejection fraction or clinical heart failure) was not related statistically to either the presence or absence of pain with exercise Various combi nations of clinical and angiographic parameters were also compared in the two groups and again no significant differences were found

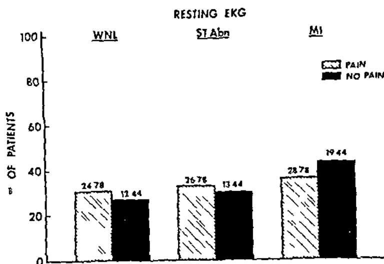


Fig 4 Frequency of various ECG findings at rest in the two subgroups of patients *WNL* = normal *ST Abn* = nonspecific ST T abnormalities *MI* = myocardial infarction

The conclusion that only the subjective recognition of ischemic pain differentiated the patients in these two groups seems to be justified by the clinical ECG and angiographic parameters that were examined but several qualifications should be considered First dyspnea has been reported to be an anginal equivalent[9] and three of the 44 pain free patients did complain of shortness of breath when they stopped their exercise test Inclusion of these patients in the symptomatic subgroup did not result in any significant differences nor would inclusion of another nine patients with fatigue as their reason for stopping the test We are still left with 32 patients (or 26% of the total group) without overt symptoms—assuming the veracity of their histories Second it is possible that had all patients been exercised on a more rigorous exercise protocol more would have experienced symptoms The difference probably would not have been marked however since Bartel and associates [6] using graded treadmill tests reported 17% pain free coronary patients with positive tests Third we did not conduct pain threshold tests to determine if our pain free group actually had a higher than normal pain threshold Fourth patients may have experienced truly unusual anginal equivalents without either they or the investigators being aware of them Finally blood pressure determinations during exercise were not available in most patients and thus differences in pressure-rate products between the two groups could not be compared These qualifications notwithstanding our results and those of the Duke University series[10] (as well as the studies dealing only with asymptomatic individuals[2 4]) indicate that a considerable number of patients with coronary disease may have ECG evidence of exercise induced myocardial ischemia without angina or its usual equivalents These studies plus those employing ambulatory ECG monitoring to detect ischemic heart disease [1] suggest that in some patients the anginal warning system (resulting from a combination of humoral neural and psychologic factors) is temporarily or permanently defective The presence of such a defective warning system may help to explain why the initial manifestation of coronary artery disease in some individuals is myocardial infarction or sudden death and why identification of such individuals before the occurrence of a morbid event can be difficult [3]

Summary

Although many patients with coronary artery disease (CAD) have a positive exercise test without pain the frequency and significance of this silent ischemia is unclear Therefore we studied 122 consecutive clinically stable patients with angiographically defined CAD (> 75 per cent luminal stenosis) and a positive exercise test Seventy eight patients had pain or anginal equivalent during or after a positive exercise test 44 did not including 32 (26 per cent) with no symptoms at all Patients were evaluated as to age sex

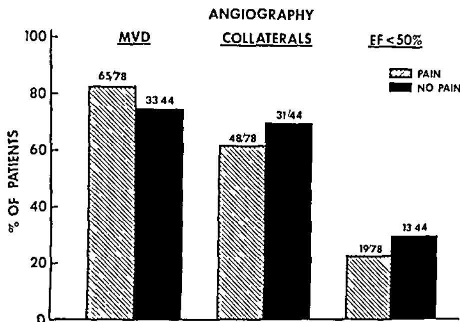


Fig 5 Frequency of multivessel disease (*MVD*) collateral vessels and poor ventricular function in the two subgroups of patients *EF* = ejection fraction

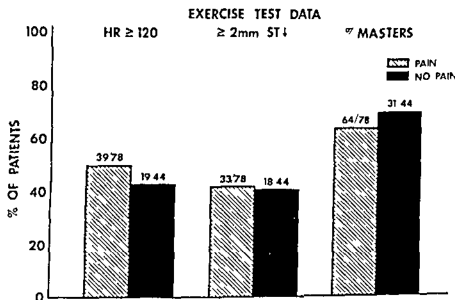


Fig 6 The two subgroups are compared for frequency of maximum heart rate > 120 beats/minute with exercise markedly positive post exercise ECG (> 2 mm ST segment depression) and two step (Master's) testing

prior myocardial infarction congestive failure, hypertension diabetes mellitus, and digoxin or propranolol therapy—in addition to anginal symptoms before during or after the exercise itself Extent of CAD presence of collaterals and left ventricular ejection fraction were also determined All exercise tests were evaluated for evidence of ST T abnormalities or prior infarction on the control ECG as well as peak heart rate during exercise and post exercise degree of ST segment depression There were no significant differences between patients with and without exercise induced pain in regard to any of the clinical and angiographic features noted above

demonstrating that silent myocardial ischemia during or after exercise testing is not uncommon and is not readily attributable to any obvious clinical or catheterization findings Further studies are necessary to determine if patients with evidence of "silent myocardial ischemia are especially prone to sudden death

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Bacterial endocarditis An analysis of factors affecting long-term survival

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In a review of the experience with bacterial endocarditis at the University of Mississippi Medical Center (UMMC) during the interval 1955 to 1959 Jackson and Allison[1] reported that only 50 per cent of their patients survived 12 months or longer, a figure well below the 90 per cent given by Weinstein and Rubin[2] in a recent report It was of interest, therefore, to study the more recent experience at the UMMC It is the purpose of this paper to report some aspects of the experience with bacterial endocarditis in adults who were treated in the UMMC during the interval from January 1, 1960 through June 30 1974 Emphasis is placed on analysis of factors related to prognosis

Material and methods

The individuals included in this study were all admitted to the medical wards of the UMMC during the interval from January 1, 1960 until July 30 1974 The diagnosis of bacterial endocarditis was considered adequately documented for the purposes of this study if bacteria were recovered from the blood and the clinical picture was suggestive or if in the presence of sterile blood cultures the clinical picture was classic, or if there was confirmation by autopsy Cases were excluded if the patient s condition one year after admission to the UMMC was unknown

A total of 194 cases were obtained by review of the records of the infectious disease division from discharge diagnoses and by review of all autopsies performed during the study period A total of 113 patients met our criteria but, of these five represented endocarditis that occurred after cardiac surgery and were eliminated Six patients having received no treatment, were diagnosed at autopsy, leaving a total of 102 treated cases

Follow up data until time of death or end of the study were obtained on all 102 patients who were felt to have adequate confirmation of bacterial endocarditis, but as the earlier patients were followed much longer than those treated in the last few years of the study, emphasis will be on the status of the individual one year after the diagnosis was made These patients were then examined relating longevity from the time of illness to the following (1) infecting organisms (2) age at time of diagnosis, (3) sex of patient, and (4) the presence of pre existing heart disease Autopsy data (36 patients) were examined with emphasis on valve involvement, pre existing heart disease, and complications of endocarditis

Treatment

Each patient received an antimicrobial regimen appropriate for the treatment of endocarditis When the organism was known the antimicrobial drugs were selected on the basis of the sensitivities as measured in the laboratory In as much as penicillin sensitive organisms were isolated most often, most patients were treated with intravenously administered penicillin G plus intramuscular streptomycin When the organism was not recovered from the bloodstream, large doses of penicillin G plus streptomycin were used Bacteriological cure as shown by disappearance of bacteria from the blood plus defervescence and

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other signs of clinical improvement was achieved in most cases In two individuals therapy was not successful in erradicating the infecting organism One of these a 37 year old white female with enterococcal disease died after 142 days of treatment that included penicillin G vancomycin ristocetin streptomycin erythromycin tetracycline and chloramphenicol in several combinations The other a 62 year old white male with *Streptococcus viridans* disease was treated for 37 days with penicillin G streptomycin and probenicid but 14 days later the organism was again present in his blood An additional 43 days of treatment resulted in clearing the infection but he died of congestive heart failure six months later A third patient addicted to heroin deserted three times prior to completion of her regimen for treatment of *Staphylococcus aureus* disease and was finally treated for six consecutive weeks with methicillin plus streptomycin She died eight years later but the cause of her death is unknown

Results

Over all 26 patients died within 30 days of admission and an additional 32 patients died within the first year after the onset of their illness Thus a total of 58 patients or 56 per cent of the group died in the first 365 days leaving only 44 individuals or 44 per cent as survivors

Seventeen different infecting organisms were identified in the 102 patients studied The number of patients infected with each organism and the number of these surviving at least for one year are seen in Table I Five patients had multiple organisms identified on blood cultures while 16 patients had negative blood cultures

Fig 1 relates one year survival in 88 patients with frequently encountered organisms Of all patients with alpha hemolytic Streptococcus identified on blood culture approximately 72 per cent survived one year whereas only 27 per cent of patients with *Staphylococcus aureus* survived one year and 50 per cent of patients with Enterococcus identified on blood culture survived one year Of the four patients with *Staphylococcus epidermidis* identified on blood culture none were alive after 365 days Sixteen patients had no organisms identified on blood culture and of these five patients or 31 per cent were alive at one year Five patients had multiple organisms identified on blood culture and all five were alive after 365 days

Table I Results of blood cultures from 102 cases of bacterial endocarditis

Organism	*Number times recovered*	*Number of patients surviving 365 days*
Streptococcus viridans	32	12
Enterococcus	10	3
Staphylococcus aureus	15	4
Staphylococcus epidermidis	4	0
Streptococcus mutans	1	0
Pseudomonas	2	0
Group A beta Streptococcus	2	0
Herellea	1	0
Pneumococcus	4	1
Non hemolytic Streptococcus	3	0
Anaerobic non hemolytic Streptococcus	1	1
Escherichia coli	1	0
Proteus species	1	1
Corynebacterium	1	1
Diphtheroid	1	1
Streptococcus salivarius	1	1
Hemophilus parainfluenzae	1	1
None	16	4
Multiple organisms†	5	3

Previously reported
†Identities included in list above

Pre-existing heart disease Pre existing heart disease was present in a group of 97 patients In Fig 2 this is related to the infecting organism It is seen that 94 per cent of patients with alpha hemolytic streptococcus identified on blood culture had pre existing heart disease All 10 patients with Enterococcus documented as the infecting organism were found to have pre existing cardiovascular disease Sixty seven per cent of patients with *Staphylococcus aureus* endocarditis had a prior history of heart disease whereas 94 per cent of patients with no organism identified had prior heart disease Seventy one per cent of those with other organisms had prior heart disease Two of the four patients with multiple organisms identified on blood culture had prior heart disease

Rheumatic heart disease accounted for 75 per cent of the patients identified with pre existing heart disease whereas congenital heart disease accounted for 9 per cent Other forms of heart

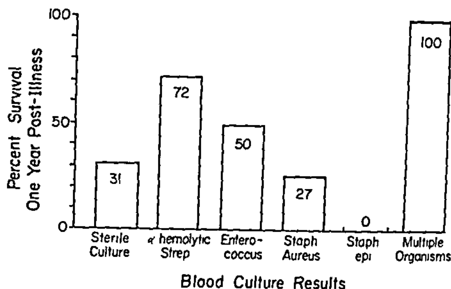


Fig 1 Per cent surviving one year vs causative organism in 102 cases of bacterial endocarditis

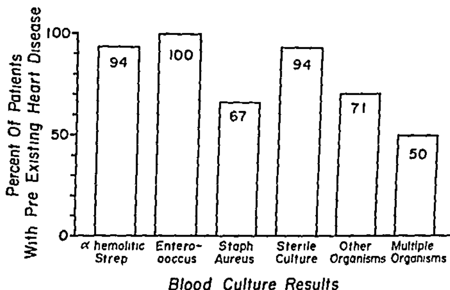


Fig 2 The per cent of the patients with pre existing heart disease is shown vs the causative organism in 102 cases of bacterial endocarditis

disease mostly arteriosclerotic and hypertensive heart disease accounted for 12 per cent

Longevity vs sex of patient Fig 3 reflects relationship of the sex of the patient to survival time Of the 58 males (average age 44 6 years) and 43 females (average age 35 2 years) represented it is noted that an almost identical percentage died in the first 30 days of their illness Thirty two per cent of males and 33 per cent of females died during this time At six months 48 per cent of males and 58 per cent of females remained alive This 10 per cent difference remained until approximately the fourth year of follow up with both groups experiencing approximately 7 per cent mortality per year By the fifth year of follow up 19 per cent of the original group of males and 20 per cent of the females remained alive Both groups continued to experience 3 per cent mortality yearly with 6 per cent of females and 2 per cent of males being alive in the eleventh year after their illness

Longevity vs age at time of illness The 102 patients are grouped according to age in Fig 4 Twelve per cent of patients were from 16 to 19 years old Twenty per cent were in their third decade at the onset of their illness Eighteen per cent were 30 to 39 years of age and 17 per cent were 40 to 49 years old The sixth decade represented 14 per cent of the total group Twelve per cent were 60 to 69 years old, and 6 per cent of the entire group was greater than seventy years old

It was noted above that in this group of 102 patients the over all one year survival was found to be 44 per cent When this was examined in

relation to age at the time of illness it was observed that the highest one year mortality occurred in the fifth and sixth decades with 37 per cent and 21 per cent surviving respectively The seventh decade representing 12 per cent of the total was found to have 42 per cent one year survivors while the lowest mortality was found in the third decade with 67 per cent surviving one year Both the 16 to 20 year age group and the greater than 70 year age group had identical one year survivals of 50 per cent The fifth decade had 53 per cent survivors

Autopsy data Autopsy data was available for 36 patients In these patients postmortem cultures confirmed antemortem cultures in 25 per cent In another 11 per cent the organism was isolated only at time of autopsy

The mitral valve was found at autopsy to be involved in 33 per cent of the cases, the aortic valve in 33 per cent of the cases and both aortic and mitral valve in 26 per cent of the cases In one patient only the left atrium was involved while another patient had involvement of both the aortic and tricuspid valves

Pre existing rheumatic valve disease was noted in 22 per cent of the autopsies while the presence of arteriosclerotic heart disease was documented in 17 per cent of the autopsy protocols

An acute myocardial infarct was noted in six of the autopsied patients and emboli were noted in the coronary arteries of four of these patients Pulmonary edema liver congestion and other autopsy findings compatible with congestive heart failure were found in 42 per cent of the autopsies There were emboli in the vessels to the kidney spleen and other sites in 61 per cent of autopsies Glomerulonephritis was described in only 19 per cent of the autopsied patients

An accompanying meningitis was noted in three patients One case of myocardial abscess and one of myocarditis were described

Discussion

Weinstein and Rubin[1] have stated that the survival in infective endocarditis approaches 90 per cent Others have stated that 82 per cent of patients followed for five years after discharge remained alive In our group of 102 patients the survival rates both at one year and at the end of a 14 year follow up period were much lower than in these reports We found a 1 year mortality rate of 56 per cent which is quite similar to the 50 per

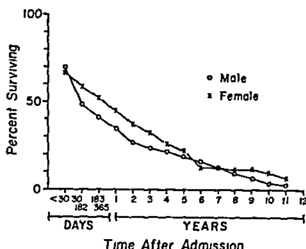


Fig 3 Males and females were nearly equally represented (58 and 43 respectively) The difference in deaths during the 5 years after admission is probably accounted for by the men being slightly older than the women

cent mortality rate reported by Jackson and Allison in an earlier study at this institution and compares closely with the 45 per cent survival rate reported by Mills and associates[4]

Thirty three per cent of our patients were infected with *Streptococcus viridans* These patients had a 72 per cent one year survival rate A recent review[2] has noted that the incidence of *Streptococcus viridans* endocarditis presently seems to account for 35 per cent to 48 per cent of all patients with endocarditis This contrasts with 79 per cent of cases of infective endocarditis due to this organism in the pre antibiotic era In a review in 1962 Vogler and colleagues found 73 per cent of patients with *Streptococcus viridans* to be hospital survivors This is compared to 69 per cent of our patients who were one year survivors However after 11 years follow up it is interesting that only 36 per cent of our patients with *Streptococcus viridans* endocarditis remained alive This may represent the severity of the underlying valvular disease which 93 per cent of patients with *Streptococcus viridans* were believed to have

Previous studies have shown a striking increase in survival of patients with *Streptococcus viridans* and in those with sterile blood cultures during the antibiotic era[2] With the exception of those patients infected with *Staphylococcus epidermidis* our highest mortality rate was observed in the group of patients with sterile blood cultures Only 28 per cent of these patients

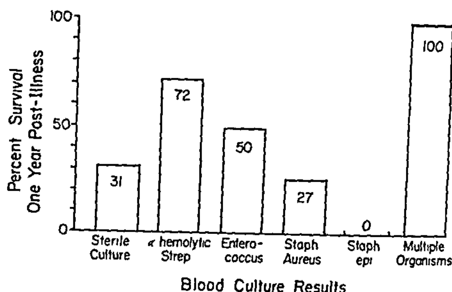


Fig 1 Per cent surviving one year vs causative organism in 102 cases of bacterial endocarditis

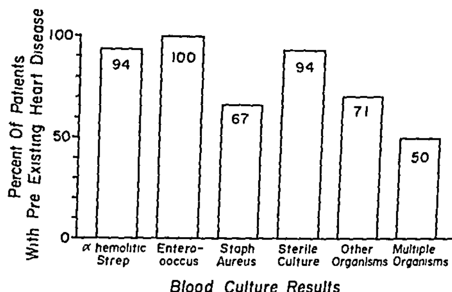


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It was noted above that in this group of 102 patients the over all one year survival was found to be 44 per cent When this was examined in

those individuals with bacterial endocarditis treated in one large medical center during the period January 1960 to June 1974 was poor over all with approximately 56 per cent dying within the first year after diagnosis The deaths were due to either heart failure or complications secondary to embolic phenomena Recently several patients have undergone valve replacement in an effort to avoid seemingly certain death from progressive cardiac failure We as others believe the prognosis is thereby improved but long term follow up will be required to study the effect of this approach

Summary

The records of 108 patients treated for bacterial endocarditis were reviewed Six were diagnosed at autopsy and had not been treated for endocarditis Of the 102 treated patients 32 died during the first 30 days and 32 more were dead by 365 days Although some reports indicate a much greater survival rate our findings are more in keeping with those reports giving a rather poor long term outlook for patients with endocarditis

We thank Mr Al Sheffield of the Division of Public Health Statistics of the Mississippi State Health Department Miss Betty Ezelle of the UMMC and many social workers and nurses of the State Health Department for their assistance

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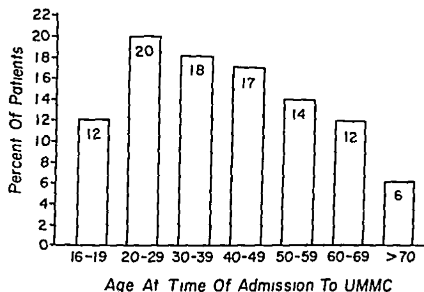


Fig 4 Age at time of admission of patients with bacterial endocarditis shows the disease present in all age groups studied with most cases during the third fourth and fifth decades

survived one year after hospitalization It should be noted that anaerobic cultures were not obtained consistently and this may account for some of the negatives Previous studies have shown the incidence of heart failure to be 60 per cent in patients with sterile blood cultures [4] Of 19 patients with sterile blood cultures reported by Vogler and colleagues [3] there were seven or 36 per cent hospital survivors This high mortality rate may be attributed to the difficulty in selection of and the delay in starting adequate antimicrobial therapy under such circumstances

Only 33 per cent of patients with *Staphylococcus aureus* in the present study survived one year after hospitalization Prior to 1950 no survivors of *Staphylococcus aureus* endocarditis were noted [2] Two recent reviews have shown the hospital survival of patients with *Staphylococcus* endocarditis to be approximately 30 per cent to 40 per cent[2, 4] with a 35 per cent incidence of severe heart failure developing within six months of the onset of illness

All four of our patients with *Staphylococcus epidermidis* endocarditis died within the first year It is noted by Weinstein and Rubin[2] that infection with *Staphylococcus epidermidis* was practically unknown prior to the antibiotic era and is usually seen in patients with underlying rheumatic heart disease

One year survival of the eleven patients with enterococcal endocarditis was observed to be 50 per cent Other observers have noted 77 per cent hospital survivors in a group of 13 patients with enterococcal endocarditis[3] and an incidence of heart failure approaching 100 per cent in these patients

It was surprising that all five of the patients with multiple organisms on blood culture survived the first year The cause for this seemingly paradoxical observation is not known

As stated above, 99 of the 108 patients included in this review had pre existing heart disease Rheumatic heart disease accounted for 77 per cent, while congenital heart disease accounted for only 9 per cent

The slightly higher mortality rate of males throughout the follow up period may be explained by the observation that the average age of the males was approximately 10 years greater than that of the females

When the mortality figures are compared with the age of the patient at the time of illness, it can be seen that the highest mortality rate occurred in the sixth decade Although this could be expected with advancing age only 37 per cent of the patients aged 30 to 39 years survived one year after hospitalization Perhaps a more severe form of valvular disease in younger individuals could account for this descrepancy The third decade had the highest percentage of one year survivors and the lowest attrition rate although it should be noted that only three of 21 original patients survived at the end of the study In evaluating these findings it should be noted that some of the 25 survivors in all age groups were less than five years post diagnosis at the completion of the study period

Our observations showed that the outlook for

exercise blood pressure and heart rate were recorded at minute intervals Respiratory function tests were performed on the day of testing The current chest x ray was compared to the immediate preoperative film

The difference among the mean F A I values of the etiological groups and for valve types were tested using the Wilcoxon ranked sum test A correlation coefficient was calculated for the relationship of F A I and time since operation

Results

The results of F A I for the three etiological groups have been plotted in Fig 1 The mean F A I for the Q fever group was 9 6 ± 12 1 for the bacterial endocarditis group it was 24 1 ± 14 6 and for the rheumatic fever group it was 24 8 ± 10 5 The values for the Q fever group are significantly better than values for either the endocarditis group (p < 0 5) or the rheumatic fever group (p < 05)

The following mean F A I values were obtained from the valve types Braunwald Cutter 15 1 ± 8 1 homograft 28 1 ± 22 1 fascia lata 24 8 ± 6 Lillehei Kaster 12 7 ± 16 No significant difference was found between any of the groups No correlations was found between the time since operation and F A I There was no difference in blood pressure or heart rate response for the three groups

The mean pre and postoperative cardiothoracic ratios for each group are shown in Table I

The respiratory function tests were within normal limits for all patients thus excluding a respiratory cause for impaired maximal oxygen uptake

Discussion

There is a clear difference in exercise capacity between the groups of patients who had Q fever endocarditis and those groups who had had bacterial endocarditis and rheumatic fever

There is substantial evidence that permanent myocardial damage occurs as a direct consequence of bacterial endocarditis Autopsies of patients suffering from bacterial endocarditis frequently show microemboli scattered focal myocardial abscesses or diffuse interstitial myocarditis Animal experiments have shown that the enzymes produced by bacteria responsible for the endocarditis are capable of causing a myocarditis and eventual fibrosis [1] Acute experimental endocarditis is associated with mononuclear cell infiltrate and muscle degeneration in the myocardium associated with hemodynamic impairment [12]

In rheumatic fever endocardium myocardium and pericardium can be involved in the acute stage most commonly all three in combination Myocardial involvement can cause serious cardiac disability in heart failure in the acute stages Aschoff bodies the histologic hallmark of rheumatic fever are found principally in the interfascicular fibrous septa and in the connective tissue around blood vessels Eventually these proliferative lesions are replaced by fibrous tissue so that

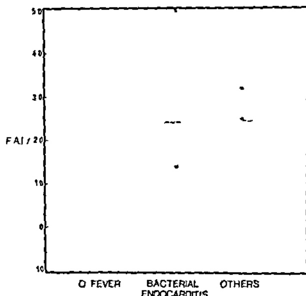


Fig 1 The functional aerobic impairment *(F A I)* values have been plotted for the three etiological groups *The horizontal bars* indicate the mean of each group

Table I Pre and postoperative cardiothoracic ratios for each group

Etiology	*Cardiothoracic ratio*		
	Preoperative	*Postoperative*	*Mean difference (± std error)*
Q fever*	56	47	09 ± 02
Bacterial endocarditis	57	46	10 ± 0?
Others	.57	51	06 ± 01

The ratio of mean change to its standard error for all three groups was to the order of five

Influence of etiology on the functional result of aortic valve replacement

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Surgical intervention in symptomatic aortic incompetence improves longevity when compared with the natural history of the disease[1,2] The success of the operation in most reports has been based upon late survival statistics and cardiac functional classification before and after surgery[3-5] More detailed postoperative assessment of patients following aortic valve replacement for isolated aortic incompetence has revealed residual left ventricular impairment[6] Preoperative factors shown to influence late survival are cardiac size, congestive cardiac failure, and ventricular premature beats[4,7]

In this study the effect etiology had on the functional result of aortic valve replacement for isolated aortic incompetence was examined Maximal exercise testing on a treadmill was used as a means of comparison

Methods and Materials

Twenty five patients were studied All patients had previously had aortic incompetence as their only valve lesion which had been assessed as severe They were divided into three groups on an etiological basis Seven had suffered from Q fever endocarditis, nine from bacterial endocarditis and a third group comprised eight patients who had suffered rheumatic valvular disease and one patient who had aortic wall disease associated with hypertension

The diagnosis of Q fever endocarditis was confirmed in each case by culturing *Coxiella burneti* in guinea pigs innoculated with valve material removed at operation

The duration of signs and symptoms before surgery in the Q fever and rheumatic group ranged between three months and 15 years the mean in both groups being 7 6 years Seven of the nine patients in the bacterial endocarditis group had a very short duration of symptoms prior to valve replacement

At operation a variety of valves were used They included eight Braunwald Cutter prosthetic valves seven homografts, six fascia lata and four Lillehei Kaster prosthetic valves At the time of testing all valves were competent and no patient had clinical or radiological evidence of heart failure There was no evidence of ischemic heart disease

The interval between surgery and exercise testing in each group was

Q fever endocarditis—6 months to 52 months (mean 26 months)

Bacterial endocarditis—17 months to 60 months (mean 31 months)

Others—10 months to 64 months (mean 36 months)

Treadmill exercise testing was carried out according to the Bruce protocol[8] All patients were exercised maximally, the indications for termination of exercise were, dizziness dyspnea leg fatigue or multiple ventricular ectopic beats No patient developed chest pain with exercise Bruce and colleagues[8] have shown that functional aerobic impairment (F A I) related to maximal oxygen uptake and hence to cardiac output

By using the appropriate nomograms[8] the F A I value was obtained from the total duration of exercise performed on the treadmill During

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Coronary artery spasm and mitral valve prolapse

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Mitral valve prolapse is a well recognized clinical entity occurring predominantly in females of virtually all ages Commonly associated symptoms include chest pain dyspnea fatigue palpitation presyncope and syncope The pathogenesis of these symptoms particularly the symptom of chest pain has remained poorly understood

Several authors [6] have suggested that an ischemic process may be a possible cause of precordial pain in some patients with mitral valve prolapse Since most individuals with this condition have normal coronary arteries at angiography [7] we considered the possibility that coronary artery spasm may produce transient myocardial ischemia in association with mitral valve prolapse The following study was therefore undertaken to examine the incidence of mitral valve prolapse in patients with chest pain who exhibited coronary artery spasm during selective coronary arteriography

Material and methods

The files of 745 patients investigated by selective coronary arteriography in the Cardiovascular Unit of Sunnybrook Medical Centre between 1969 and 1975 were reviewed for evidence of coronary artery spasm This was defined for the purposes of this study as the visualization of a segmental or diffuse area of significant reduction (70 per cent) in the coronary arterial lumen reversible either spontaneously or by the administration of vasodilating agents

Ten patients representing 1 34 per cent of all those undergoing selective coronary arteriography were shown to have reversible coronary artery spasm as above defined by sequential coronary arteriography All 10 patients had undergone investigation including right and left cardiac catheterization left ventriculography and selective coronary arteriography by Judkins technique—in that order—under mild sedation with diazepam

The coronary arteriograms were performed with Renografin 76 and angiographic images were recorded on 35 mm film at 60 frames/second In addition two of the 10 patients had angiography images recorded on 70 mm film at 4 frames/second Routine LAO and RAO projections were performed in all patients Nitrates were not administered routinely prior to coronary arteriography

The left ventricular cineangiograms were obtained in the 30 degree RAO projection

These 10 coronary arteriograms were reviewed by three independent observers for evidence of unequivocal spasm as defined above The left ventricular cineangiograms were reviewed by the same observers for abnormalities of left ventricular wall motion and evidence of mitral valve prolapse The angiographic criteria for mitral valve prolapse were based on angiographic anatomic correlations previously described [11] [13] in which prolapse of the middle scallop produced a central bulge overlying the left atrium in the RAO left ventricular cineangiogram prolapse of

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there is a diffuse increase in the amount of fibrous tissue present[13]

Coxiella burnetii, the organism responsible for Q fever is an obligate intracellular parasite[14] In the heart it is found only in the endothelial and serosal cells and does not invade the myocardial cells The organism has not been shown to produce toxins[15] In a recent review of Q fever endocarditis,[16] the indolent nature of the disease was emphasized and because of the biological properties of *Coxiella burnetii* it is unlikely to cause myocardial damage similar to that caused by bacteria

The indication for aortic valve replacement in all patients was symptomatology accompanied by severe aortic incompetence assessed by catheter study The cardiothoracic ratios indicated that the three groups were comparable on the basis of heart size There was a significant reduction in heart size following operation, but not more marked in one group than another

The preoperative duration of signs and symptoms were the same in the Q fever group and the rheumatic fever group On the other hand the bacterial endocarditis group with a very short duration of history, performed much the same as the rheumatic group These facts suggest that length of history and hence the hemodynamic abnormality is not important in the long term results of aortic valve replacement

Following the successful aortic valve replacement, long term studies show that most patients achieve an improved cardiac functional classification after surgery and maintain this for a number of years[4,5] This study confirms that there is no relationship between functional result and length of follow up

Four different types of valves were used for the valve replacement This reflects the changing approach to valve replacement in the unit Initially fascia lata valves were used but when it became apparent that these valves developed incompetence after insertion homografts and Braunwald Cutter valves were used Homografts were used in preference to prosthetic valves but the determining factor was the size of the aortic valve ring Initially Braunwald Cutter valves were used but later Lillehei Kaster valves were the prosthetic choice Although statistical analysis of the results for individual valves within etiological groups is not possible because of the small numbers it does not seem likely that there is any difference

Summary

The functional result of aortic valve replacement has been assessed in patients treated for isolated aortic incompetence Using maximal oxygen uptake as an index of myocardial function, a significant difference ($p < .05$) exists between the patients who had Q fever endocarditis on the one hand and those who had bacterial endocarditis or rheumatic fever on the other We believe that permanent myocardial damage occurs as a result of bacterial endocarditis and rheumatic fever but because of the biological properties of *Coxiella burnetii* the myocardium is spared in Q fever endocarditis

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Table II Left ventriculography data

Case number	Ventriculogram: Left ventricular wall motion	Ventriculogram: Location and degree of MVP	Coronary arteriogram: Location of spasm	Coronary arteriogram: Fixed lesions
1	Mild anterolateral hypokinesis	Mild AL and PM	Left main diffuse RCA	Nil
2	Mild apical hypokinesis Early diastolic relaxation	Moderate PM	Mid LAD	Nil
3	Mild generalized hypokinesis	None	Proximal RCA	Nil
4	Normal	Mild middle and PM	Proximal RCA	Nil
5	Inadequate long axis	Mild PM	Proximal RCA	Nil
6	Normal	Mild PM	Proximal RCA	Nil
7	Mild apical hypokinesis	Mild PM	Proximal RCA	Nil
8	Inadequate long axis shortening Mild anterior hypokinesis	Mild PM	Proximal RCA	Nil
9	Normal	Moderate AL middle and PM	Proximal RCA	50% left main
10	Mild anterior hypokinesis	Moderate PM	Proximal RCA	50% circumflex

Eight of 10 patients had otherwise normal coronary arteries One patient had a 50 per cent left main coronary artery lesion (Case 9) and one had a 50 per cent circumflex lesion (Case 10)

Discussion

Coronary artery spasm is associated with various disease entities including the syndrome of myocardial infarction with normal coronary arteries[2, 3] Prinzmetal s variant angina[3] and nitroglycerin withdrawal in munition workers[6] Occasionally this condition occurs in patients with chest pain who have normal coronary arteries at angiography In these cases the area of spasm is often within the coronary ostium suggesting that catheter trauma may be responsible for the induction of spasm in the proximal right or left main artery However it is also conceivable that certain individuals may be predisposed to the development of catheter induced spasm because of an underlying abnormality of nervous or arterial smooth muscle activity

Proximal coronary artery spasm is most often observed in patients with angina or chest pain syndromes and otherwise normal coronary arteries In these individuals, spasm may not be simply a response to local catheter trauma but a sign of abnormal arterial smooth muscle tone The occurrence of both spontaneous distal and catheter induced spasm in the same patient further suggests a pathophysiological basis for the latter event rather than a chance arteriographic curiosity

The incidence of catheter induced spasm is quite low varying between 0 26 per cent and 2 93 per cent in several studies[7, 20] It is difficult to determine the exact frequency of this phenomenon since pretreatment with nitrates catheterization techniques and patient selection may influence the development of spasm in any one series However the findings of coronary artery spasm in 1 34 per cent of patient in our study is consistent with the literature and attests to the infrequent occurrence of this event In contrast mitral valve prolapse is more common and may be seen in 6 to 21 per cent of normal females[21, 22]

Although one cannot make an exact extrapolation of these data to our own series the coincidental occurrence of mitral valve prolapse in nine of 10 patients with coronary artery spasm is indeed striking and raises the possibility of a common pathogenesis for the two conditions in some patients

It is interesting that of the 10 patients with coronary artery spasm eight had a previous history of chest pain while only two patients had evidence of haemodynamically significant coronary artery disease This observation agrees with previous reports in which coronary artery spasm whether catheter induced or spontaneous was frequently found in patients with angina or chest pain syndromes who had no fixed coronary arterial lesions implicating spasm as a cause of the pain[17, 3] The occurrence of both proximal and distal spasm in one of our patients complements

Table I Clinical and electrocardiographic features

Case number	Age & sex	History	Physical examination	ECG findings
1	38 F	Chest pain palpitations syncope	Systolic murmur	Normal resting ST elevation with chest pain
2	33 F	Chest pain	Midsystolic click	ST T changes (inferior and anterior)
3	34 M	Syncope palpitations	Midsystolic click	Normal
4	50 F	Chest pain	Midsystolic click	RBBB
5	46 M	Chest pain dyspnea	Nil	Normal
6	55 F	Fatigue	Systolic murmur	LVH & strain ST T changes (inferior and anterior)
7	42 F	Chest pain	Nil	ST T changes (anterior)
8	42 F	Chest pain dyspnea	Nil	ST T changes (anterior and inferior)
9	39 F	Chest pain	Nil	ST T changes (anterior)
10	45 F	Chest pain fatigue dyspnea	Nil	ST T changes (inferior)

the anterolateral commissural scallop produced an anterosuperior bulge, and prolapse of the posteromedial commissural scallop produced a posteroinferior bulge The degree of mitral valve prolapse was assessed as 'mild,' "moderate' or severe

The clinical findings and heart catheterization data were available for review in all 10 patients

Results

Clinical and electrocardiographic features (Table I) Of the 10 patients in this study eight were female The average age was 42 5 years (range 33 to 55 years)

Notable symptoms included chest pain in eight patients, syncope in two dyspnea in eight, palpitations in three, and fatigue in two Of the two patients with syncopal episodes and palpitations one patient (Case 1) had documented recurrent ventricular tachyarrhythmias In the other two patients with palpitations (Cases 3 and 8) no arrhythmias were documented

Five patients had a systolic click or late systolic murmur on auscultation One patient (Case 3) who had a systolic click with evidence of coronary artery spasm had no angiographically demonstrable mitral valve prolapse

Seven patients had ECG abnormalities These included ST T changes over the anterior precordial leads in two ST-T changes over the inferior leads in one, LVH and strain in one and complete right bundle branch block in one Three patients had normal ECG s One patient (Case 1) was subsequently found to have ST segment elevation coinciding with episodes of chest pain suggesting Prinzmetal s variant angina In this particular patient coronary artery spasm and mitral valve prolapse were demonstrated

Two patients (Cases 1 and 9) underwent exercise ECG testing Both patients had positive exercise tests

Left ventriculography (Table II) Abnormalities of left ventricular wall motion were common in our series occurring in seven of 10 patients These findings are summarized in Table II and include *mild anterolateral hypokinesis in* one patient mild apical hypokinesis in two early diastolic anterior relaxation in one, inadequate long axis shortening in two, mild anterior hypokinesis in two and mild generalized hypokinesis in one Three patients showed normal left ventricular wall motion

Significantly, nine of 10 patients had evidence of mitral valve prolapse This involved the posteromedial scallop in six patients the anterolateral and posteromedial scallops in one (Fig 6) the middle and posteromedial scallops in one and the anterolateral middle and posteromedial scallops in one (Fig 3)

Coronary arteriography (Table II) There was documented coronary artery spasm in all 10 patients in this series This involved the proximal right coronary artery in eight (Figs 1 and 2) the mid LAD in one, and the *left main* coronary artery in one (Figs 4 and 5) Of the 10 patients with coronary artery spasm eight patients had evidence of catheter induced spasm one patient had spontaneous spasm and one patient had both spontaneous and catheter induced spasm



Fig 3 Left ventriculogram of the same patient (Case 9) with evidence of prolapse involving the anterolateral *(black arrow)* middle *(white arrow)* and posteromedial scallop of the posterior mitral leaflet



Fig 4 Selective coronary arteriogram showing spasm of the left main coronary artery (Case 1)

may be mediated by alpha adrenergic receptors Thus it is conceivable that phenylephrine may provoke chest pain by producing coronary artery spasm in susceptible patients This observation is supported by a case report in which nitrate resistant coronary artery spasm was abolished by the alpha adrenergic receptor antagonist phentolamine

In a recent report Chesler and co workers[7] have observed four cases of mitral valve prolapse in which myocardial infarction occurred Surprisingly post infarction coronary arteriograms showed no evidence of organic coronary disease These authors suspected that coronary artery spasm was the cause of the myocardial infarction although no evidence of spasm was demonstrated at angiography



Fig 5 Repeat injection of the left coronary artery following nitroglycerin showing resolution of the previous spasm



Fig 6 Left ventriculogram of the patient (Case 1) with evidence of prolapse involving the anterolateral scallop slightly *(black arrow)* but mainly the posteromedial scallop of the posterior mitral leaflet

It appears that an ischemic mechanism may be a cause of chest pain in some patients with mitral valve prolapse The occurrence of myocardial infarction without demonstrable coronary disease and the apparent association between the valvular abnormality and coronary artery spasm further suggest that transient vasoconstriction may well be the cause of the cardiac symptoms and complications in certain individuals with mitral valve prolapse

Summary

Ten patients representing 1 34 per cent of those patients undergoing selective coronary arteriography were found to have unequivocal evidence of coronary artery spasm This involved the proximal right coronary artery in eight



Fig 1 Selective coronary arteriogram showing spontaneous spasm of the proximal right coronary artery (Case 9)



Fig 2 Repeat injection of the right coronary artery after intravenous phentolamine showing almost complete resolution of the previous spasm

the earlier report of Chahine and associates [9] and suggests that catheter trauma may be a less important factor than has been previously believed

In addition to pain, the symptoms of mitral valve prolapse have included dyspnea, fatigue palpitations presyncope and syncope [1] Some observers have suggested that the perception of palpitations and faintness may be the result of atrial or ventricular arrhythmias [8] Other have commented on the ischemic looking repolarization changes in the electrocardiogram [4] There have also been reports of myocardial infarction with normal coronary arteries and sudden death[11-13,25] in mitral valve prolapse patients

The symptoms experienced by this patient population and the associated cardiac abnormalities suggest that an underlying ischemic mechanism may be operative in this condition In support of this concept Natarajan and co workers [6] have demonstrated that some patients with mitral valve prolapse show abnormalities of lactate metabolism presumably the result of myocardial ischemia

Several postulates have been proposed to explain the pathogenesis of myocardial ischemia in mitral valve prolapse Barlow and Bosman [3] initially speculated that compression of the circumflex artery by the dilated posterior leaflet could produce myocardial ischemia but subsequent studies failed to demonstrate any distortion of this vessel [6,9,10] Some observers have suggested a possible association between actual coronary artery disease and mitral valve prolapse to explain the cardiac symptoms but this relationship appears to be fortuitous and of no etiological importance [5]

The possibility that an ischemic focus in the papillary muscle may be produced by increased papillary muscle stress resulting from the billowing scallops has also been considered [14] In support of this concept Le Winter and colleagues have shown that intravenous phenylephrine may induce chest pain in patients with mitral valve prolapse These authors have suggested that phenylephrine by increasing systolic arterial pressure, may produce a discrepancy between myocardial oxygen supply and demand in the papillary muscle under increased tension and thus lead to chest pain Their data further suggest that chest discomfort associated with mitral valve prolapse is organic in nature and probably not entirely functional as proposed by others

There is however an alternative mechanism for phenylephrine induced chest pain in mitral valve prolapse patients This agent is also a potent alpha adrenergic receptor agonist and has been shown to produce coronary artery constriction in vivo and in vitro [28] Yasue and associates [9,30] have suggested that severe spasm of large coronary arteries in Prinzmetal's angina



Fig 3 Left ventriculogram of the same patient (Case 9) with evidence of prolapse involving the anterolateral *(black arrow)* middle *(white arrow)* and posteromedial scallops of the posterior mitral leaflet



Fig 4 Selective coronary arteriogram showing spasm of the left main coronary artery (Case 1)



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Electrode position effects on Frank lead electrocardiograms

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In electrocardiography the electrical potentials obtained from precordial electrodes depend to a great extent on the precise location of these electrodes One of the goals of every proposed lead system is to specify as precisely as possible the location of electrodes relative to well defined anatomic landmarks In doing this it is anticipated that the variability of electrocardiographic potentials unrelated to variations in the electrical activity of the heart will be reduced

In the original description of his lead system Frank[1] specified that the location of all chest and back electrodes be at the level of the fifth interspace at the sternal border for sitting or standing subjects Subsequently Langner and co workers[2] proposed that the fourth interspace be used when applied to recumbent subjects This recommendation resulted from the better agreement they obtained when comparing the Frank system to Schmitt and Simonson s SVEC III system[3] Since then some laboratories have used the fourth interspace and others have continued to use the fifth interspace for Frank electrode locations

Recently there has been a great interest in recording both Frank and the conventional 12 leads using a single recording procedure The typical recording equipment includes a patient cable having all leads necessary for applying electrodes of both systems at the same time Thereafter manual or automatic switching is used to record three leads at a time until all 15 have been recorded To reduce the number of necessary electrodes many investigators have used the location for standard lead V_6 and Frank lead A interchangeably Additionally the electrode for standard lead V_4 has become acceptable by some as Frank electrode C

Precise electrode locations according to accepted definitions for conventional precordial leads and Frank leads with relation to rib structure are depicted in Fig 1 In this illustration Frank lead locations using the fourth and fifth intercostal space levels are shown In the application of the Frank system all chest electrodes must be located at the same horizontal level which is the fifth (or fourth) intercostal space at the left sternal border It should be noted that the curvature of the rib cage is responsible for the unpredictable and sometimes large discrepancy between V_6 and A electrode positions in individuals

This study reexamines the influence of the fifth versus the fourth interspace for supine subjects and the use of a modified Frank lead system which substitutes V_4 for C Results of electrocardiographic measurements are reported for four different variations of electrode placement

Materials and methods

Electrocardiographic records were obtained from 149 adult male subjects using four different versions of the Frank system These versions will be referred to as Systems 1 2 3 and 4

System 1 Electrodes A C E, I and M applied according to Frank with all electrodes placed at

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patients, the mid left anterior descending branch in one, and the left main coronary artery in one Eight of these 10 patients had otherwise normal coronary arteries

Of these 10 patients with coronary artery spasm, nine had evidence of mitral valve prolapse This involved the posteromedial scallop in six patients the anterolateral and posteromedial scallops in one, the middle and posteromedial scallops in one, and the anterolateral, middle, and posteromedial scallops in one

These data suggest an association between coronary artery spasm and mitral valve prolapse Coronary artery spasm may thus be an important factor in the pathogenesis of the chest pain arrhythmias electrocardiographic abnormalities, and sudden death, that have already been described in some patients with mitral valve prolapse

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Electrode position effects on Frank lead electrocardiograms

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In electrocardiography the electrical potentials obtained from precordial electrodes depend to a great extent on the precise location of these electrodes. One of the goals of every proposed lead system is to specify as precisely as possible the location of electrodes relative to well defined anatomic landmarks. In doing this it is anticipated that the variability of electrocardiographic potentials unrelated to variations in the electrical activity of the heart will be reduced.

In the original description of his lead system Frank[1] specified that the location of all chest and back electrodes be at the level of the fifth interspace at the sternal border for sitting or standing subjects. Subsequently Langner and co workers[2] proposed that the fourth interspace be used when applied to recumbent subjects. This recommendation resulted from the better agreement they obtained when comparing the Frank system to Schmitt and Simonson s SVEC III system.[3] Since then some laboratories have used the fourth interspace and others have continued to use the fifth interspace for Frank electrode locations.

Recently there has been a great interest in recording both Frank and the conventional 12 leads using a single recording procedure. The typical recording equipment includes a patient cable having all leads necessary for applying electrodes of both systems at the same time. Thereafter manual or automatic switching is used to record three leads at a time until all 15 have been recorded. To reduce the number of necessary electrodes many investigators have used the location for standard lead V_6 and Frank lead A interchangeably. Additionally the electrode for standard lead V_4 has become acceptable by some as Frank electrode C.

Precise electrode locations according to accepted definitions for conventional precordial leads and Frank leads with relation to rib structure are depicted in Fig 1. In this illustration Frank lead locations using the fourth and fifth intercostal space levels are shown. In the application of the Frank system all chest electrodes must be located at the same horizontal level which is the fifth (or fourth) intercostal space at the left sternal border. It should be noted that the curvature of the rib cage is responsible for the unpredictable and sometimes large discrepancy between V_6 and A electrode positions in individuals.

This study reexamines the influence of the fifth versus the fourth interspace for supine subjects and the use of a modified Frank lead system which substitutes V_4 for C. Results of electrocardiographic measurements are reported for four different variations of electrode placement.

Materials and methods

Electrocardiographic records were obtained from 149 adult male subjects using four different versions of the Frank system. These versions will be referred to as Systems 1 2 3 and 4.

System 1 Electrodes A C E I and M applied according to Frank with all electrodes placed at

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patients, the mid left anterior descending branch in one, and the left main coronary artery in one Eight of these 10 patients had otherwise normal coronary arteries

Of these 10 patients with coronary artery spasm, nine had evidence of mitral valve prolapse This involved the posteromedial scallop in six patients the anterolateral and posteromedial scallops in one, the middle and posteromedial scallops in one and the anterolateral, middle, and posteromedial scallops in one

These data suggest an association between coronary artery spasm and mitral valve prolapse Coronary artery spasm may thus be an important factor in the pathogenesis of the chest pain, arrhythmias electrocardiographic abnormalities, and sudden death, that have already been described in some patients with mitral valve prolapse

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Experimental and laboratory reports

Electrode position effects on Frank lead electrocardiograms

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Recently there has been a great interest in recording both Frank and the conventional 12 leads using a single recording procedure The typical recording equipment includes a patient cable having all leads necessary for applying electrodes of both systems at the same time Thereafter manual or automatic switching is used to record three leads at a time until all 15 have been recorded To reduce the number of necessary electrodes many investigators have used the location for standard lead V_6 and Frank lead A interchangeably Additionally the electrode for standard lead V_4 has become acceptable by some as Frank electrode C

Precise electrode locations according to accepted definitions for conventional precordial leads and Frank leads with relation to rib structure are depicted in Fig 1 In this illustration Frank lead locations using the fourth and fifth intercostal space levels are shown In the application of the Frank system all chest electrodes must be located at the same horizontal level which is the fifth (or fourth) intercostal space at the left sternal border It should be noted that the curvature of the rib cage is responsible for the unpredictable and sometimes large discrepancy between V_6 and A electrode positions in individuals

This study reexamines the influence of the fifth versus the fourth interspace for supine subjects and the use of a modified Frank lead system which substitutes V_4 for C Results of electrocardiographic measurements are reported for four different variations of electrode placement

Materials and methods

Electrocardiographic records were obtained from 149 adult male subjects using four different versions of the Frank system These versions will be referred to as Systems 1 2 3 and 4

System 1 Electrodes A C E I and M applied according to Frank with all electrodes placed at

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Table I Mean standard deviation and 96 percentile range for selected amplitudes and durations for 149 subjects

	Fifth interspace						*Fourth interspace*					
	System 1			*System 2*			*System 3*			*System 4*		
	Mean	*Std dev*	*96% range§*	*Mean*	*Std dev*	*96% range*	*Mean*	*Std dev*	*96% range*	*Mean*	*Std dev*	*96% range*
Q,†	−043		0 to −19	−035		0 to −14	−047		0 to −19	−041		0 to −17
R,	1 13	56		1 04	53		1 18	58		1 13	56	
S	−12		0 to −45	−13		0 to −50	−12		0 to −45	−13		0 to −49
T	.0 0	18		081	18		082	20		085	19	
P max	049		0 to 095	046		0 to 087	055		0 to 10	055		0 to 10
Q	−33		0 to −80	−.32		0 to −82	−.30		0 to −.80	−32		0 to −80
R,	84	49		93	54		.89	50		93	55	
T	−18		0 to −44	−20		0 to −47	−20		0 to −50	−.20		0 to −48
P	027		0 to 0 9	078		0 to 083	031		0 to 075	030		0 to 080
P	−038		0 to −085	−040		0 to −082	−035		0 to −073	−038		0 to −075
QRS Spat. Max	1 55	.58		1 57	58		1 59	60		1 59	.59	
P Spat Max	1		0 to 23	12		0 to 21	18		0 to 19	12		0 to .20
T Spat Max	29		0 to 58	31		0 to 61	32		0 to 57	32		0 to 60
Q, Dur‡	8 0		0 to 23	7 0		0 to 21	8 0		0 to 25	8 0		0 to 23
Q, Dur	31 0		0 to 57	30 0		0 to 51	28 0		0 to 48	29 0		0 to 50

System 1 = Frank System fifth interspace System 2 = Frank system fifth interspace, except V used in place of Frank electrode C System 3 = Frank system, fourth intersp ce Syst m 4 = Frank system, fourth interspace except V used in place of Frank elertrode C

†Amplitudes are in milli olts.

‡Durati ns are in msec.

§Ranges are gi en f r measurements with skewed distributi ns.

Amplitudes and durations Means standard deviations and 96 percentile ranges for each amplitude and duration measurement for each electrode system are listed in Table I The large overlap in measurement ranges from one system to another is undoubtedly in part due to the inhomogeneity of the sample i e normal and abnormal groups included together For those measurements which are normally and nearly normally distributed the t statistic showed no significant difference at the 0 05 level between the means of System 1 and each of the other systems

For many subjects individual differences in amplitudes were not uncommon This kind of information is summarized in Table II in which only differences exceeding both 0 10 millivolt and 10 per cent of System 1 values were considered This table clearly shows that differences are least when Systems 1 and 2 are compared When V is substituted for C the trend toward decreasing R and increasing R is clear This trend remained the same even when all electrodes were shifted to the fourth interspace as may be seen when comparing Systems 1 and 4 For a level shift upward without substituting V for C both R and R increased in approximately twice as many cases as they decreased T amplitude changes occurred less frequently than those in QRS System 3 showed these changes most but even then such changes occurred in less than 10 per cent of the records

Orientations Angular mean values and mean angular deviations shown in Table III were calculated according to the methods suggested by Batschelet[a] A mean vector for all subjects is determined by obtaining mean values of sines and cosines The polar angle of the mean vector is called the mean angle A measure of dispersion called the mean angular deviation is calculated as

$$S = \sqrt{2(1\ r)}$$

where r' is the mean angle with both r and S in radians

The mean elevation angle remained essentially unchanged for all four electrode systems Azimuth mean angles remained almost un changed for Systems 2 3 and 4 all being about 8 degrees different from that of System 1 However mean angular deviation was close to 40 degrees for all four systems so that differences in the mean angle are not clearly significant

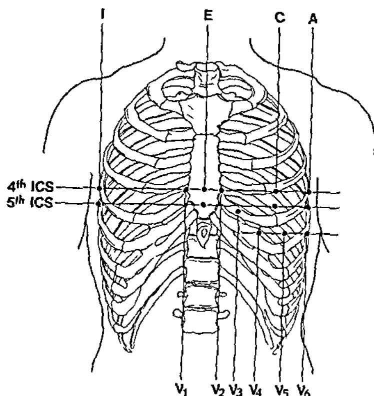


Fig 1 Electrode locations for standard precordial and Frank electrodes at the level of the fourth and fifth *intercostal spaces* relative to the rib cage Electrode C location must be determined using an angular measurement not shown here although it generally falls to the left of V Biologic variations in rib cage curvature may cause large discrepancies between V and A locations in individual cases

the level of the fifth interspace at the sternal border

System 2 Identical to System 1 except that standard precordial lead V_4 is used in place of electrode C

System 3 Identical to System 1 except that the level of all electrodes is at the fourth interspace at the sternal border

System 4 Identical to System 3 except that standard precordial lead V_4 is used in place of electrode C

The clinical diagnoses of the 149 subjects were determined by history and physical examination data without knowledge of electrocardiographic information[4] These diagnoses were as follows 66—Normal, 36—Coronary Artery Disease (CAD) 20—Hypertensive Cardiovascular Disease (HCVD) nine—Valvular Heart Disease nine—Pulmonary Disease eight—HCVD and CAD and one—Valvular and Pulmonary Disease

Eleven patient leads were used in addition to two leg leads and a head lead which enabled placement of all electrodes before recording started Four sequential orthogonal electrocardiograms, corresponding to each of the four systems were obtained for each patient using a four position, manually operated switch The switch allowed the same Frank resistor network and three preamplifiers to be used for each recording Each recording consisted of a calibration signal plus 20 seconds of electrocardiographic signal on three channels of FM magnetic tape

Becton Dickinson type 7901 silver/silverchloride electrodes with 11 mm diameter were used. Electrode wells were filled with electrode paste before application Buffer amplifiers provided no less than 50 megohms input impedance for each patient input lead Electrode positions were marked with patients supine

The data were processed utilizing the Veterans Administration electrocardiographic analysis program[5] using a Control Data Corporation 3?00 computer Details of analog to digital conversion wave recognition and measurements have been published previously,[4] and therefore only a brief summary will be presented here

The three electrocardiographic leads are each digitized at 2 msec intervals for 10 seconds after being filtered with a 200 Hz, low pass filter Wave recognition consists of identifying the beginning and end of P and QRS and the end of T using spatial velocity as the main criterion Measurements of amplitudes and durations are made on each cardiac cycle from which waves are identified Ectopic beats are discarded and average values of measurements of the remaining beats are then used

Results

To make comparisons among the four systems for each subject System 1 was selected as the baseline and results obtained from each of the other three systems were compared to it

The following sets of measurements were selected for comparison of results

Amplitudes Q, R S T P Q, R S T P QRS_m (maximum spatial QRS magnitude) P_m (maximum spatial P magnitude) and T_m (maximum spatial T magnitude)

Durations Q and Q

Orientations QRS_E (elevation angle for QRS_m) and QRS_A (azimuth angle for QRS_m)

No y lead measurements were examined because the principal electrodes (F and H) contributing to the y lead remained unchanged for all four systems

Table I Mean, standard deviation and 96 percentile range for selected amplitudes and durations for 149 subjects

	Fifth interspace						*Fourth interspace*					
	System 1			*System 2*			*System 3*			*System 4*		
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Table II Number of cases with significant amplitude changes using System 1 as reference

	System 2	*System 3*	*System 4*
Amplitude change† in R R or QRS_m	61 (41)*	104 (70)	101 (68)
R decrease	36 (24)	22 (15)	27 (18)
R increase	4 (3)	38 (26)	19 (13)
R_z decrease	5 (3)	25 (17)	16 (11)
R increase	39 (26)	46 (31)	61 (41)
QRS_m decrease	10 (7)	20 (13)	13 (9)
QRS_m increase	9 (6)	34 (23)	25 (17)
Amplitude change in T T or T_m	0	14 (9)	6 (4)
T decrease	0	2 (1)	1 (5)
T increase	0	2 (1)	1 (5)
T decrease	0	10 (7)	6 (4)
T increase	0	1 (5)	1 (5)
T_m decrease	0	1 (5)	0
T_m increase	0	7 (5)	3 (2)
No change in QRS or T amplitudes	82 (55)	34 (23)	35 (23)

Percentages of 149 subjects are shown in parentheses.

†Amplitude change is calculated as the difference between an amplitude value in Systems 2 3 or 4 with respect to its value in System 1 The change is significant if it is both greater than 0 10 millivolt and at least 10 per cent of the value in System 1

Limits of measurements Most electrocardiographic analysis programs depend on limits of one or more measurements for diagnostic classification The effect of electrode level change on normal limits was observed for 16 common measurements The results, shown in Table IV, indicate the number of records for which measurements changed from normal to abnormal or vice versa The normal limits used are those developed using the Veterans Administration data base of 510 well documented cases[8] developed for Frank leads applied at the fourth intercostal space

Electrode locations—C versus V_4 For each subject, measurements were made of the distances between C and V_4 electrodes Ranges and means of distances are presented in Table V The location of C was invariably to the left of V_4

Discussion

The effects of electrode misplacement have been studied previously,[9, 11] so it is not surprising to find that the different versions of the Frank system studied in this report also produce electrocardiographic changes Generally greater differences are produced as additional electrodes are misplaced However, the C electrode is usually the single most sensitive electrode in this respect In Table II, note that 41 per cent of the records had significant amplitude changes in R R, or QRS_m (greater than both 0 1 millivolt and 10 per cent of System 1 values) when V_4 was substituted for C When all chest electrodes were moved to the fourth interspace this number was increased to 70 per cent

The data in Table II for R_x, R_z, and QRS_m were tested for significance of differences using the Wilcoxon matched pairs signed ranks test[12] This test is useful for making judgements about the magnitude and direction of differences within pairs Application of this test demonstrated that the trends for decreasing R_z and increasing R from Systems 1 to 2 were highly significant (p = 00003) On the other hand, QRS_m changes were not significant, i e , no trend toward increasing or decreasing magnitude was evident

When comparing Systems 1 to 3, the trend for R increase was also significant (p = 02) As noted from the p values, this trend was not so strong as the R_x decreasing trend for Systems 1 to 2 However, the total number of records for which R_x changes occurred was much greater for System 3 (60 opposed to 40) Trends for R and QRS_m increases were significant at p = 006 and p = 0? levels, respectively, between Systems 1 and 3

Some general conclusions one can draw from these data are that

1 With V_4 substituted for C about 40 per cent of the records are affected by amplitude changes in R , R , or QRS_m, 25 to 30 per cent have R_z or R_z changes, and about 20 per cent have QRS_m changes In those records with changes eight to nine times as many have lower R and higher R values than vice versa and QRS_m values are equally likely to increase or decrease

2 With all electrodes shifted from the fifth to the fourth interspace, R_z R and QRS_m changes occur in about 70 per cent of the cases R is affected in about 40 per cent R_z in about 50 per cent and QRS_m in about 35 per cent of the records In those records with changes R , R_z and QRS_m increase in about two thirds and decrease in about one third of the cases However as will be noted later in this section it is difficult to predict increases or decreases in amplitudes when electrode level is shifted from the fifth to the fourth interspace

In an effort to determine if electrocardiographic changes were correlated with disease groups

Table III Means and deviations for azimuth and elevation angles for 149 subjects for four electrode systems

	Fifth interspace				*Fourth interspace*			
	System 1 (C)		*System 2 (V)*		*System 3 (C)*		*System 4 (V)*	
Angular function	*Mean angle (deg)*	*Mean angle dev (deg)*	*Mean angle (deg)*	*Mean angle dev (deg)*	*Mean angle (deg)*	*Mean angle dev (deg)*	*Mean angle (deg)*	*Mean angle dev (deg)*
Elevation‡	19 7	19 1	20 0	19 2	18 7	19 1	19 3	18 4
Azimuth†	17 5	40 0	25 9	41.2	25 7	37 6	25 3	39 2

Angular definitions are according to American Heart Association recommendations.
†Azimuth angle is in the horizontal plane and is positive for posterior angles.
‡Elevation angle is positive for inferior angles

normal subjects, HCVD patients and pulmonary disease patients were studied separately Amplitude changes for R R and QRS_m for these three groups are presented in Table VI

For both the 66 normal subjects and the 20 patients with HCVD amplitude changes with electrode shifts followed the same patterns as for all 149 subjects considered together

For the nine pulmonary disease patients some what different results were obtained For System 3 R R and QRS_m all tended to decrease in contrast to the normal subjects and HCVD patients This finding is consistent with the lower diaphragm and heart locations usually found in pulmonary disease patients as contrasted with normals To verify this observation additional patients in this group would have been useful

In a study by Draper and co workers[9] normal limits for many commonly used measurements were determined for the Frank system with electrodes applied at the level of the fourth intercostal space An appropriate question would be If these normal limits are applied how often would key measurements used for diagnostic classification change significantly when electrodes are shifted to the level of the fifth intercostal space? Table IV provides some answers For example one record having an R value outside of normal limits when recording at the level of the fifth intercostal space was recorded with a normal R value at the level of the fourth intercostal space The reverse was true for seven other subjects. This finding could have affected a diagnosis for left ventricular hypertrophy (LVH) Similarly R and (R/S) changed in 17 and 6 subjects respectively which could have affected diagnosis for LVH right ventricular hypertrophy (RVH) or chronic obstructive pulmonary disease

Table IV Changes of selected amplitude amplitude ratio and angular measurements for 149 subjects The number of subjects in which measured values changed from within normal limits to outside of normal limits or vice versa as electrode level is shifted from the fifth to the fourth intercostal space

	System 1 vs 3	
	Abn to nor	*Nor to abn*
Maximum QRS	1	2
Maximum QRS	6	10
Maximum QRS	1	6
Q	8	10
R	1	7
S	4	7
Q	5	9
R	9	8
J	3	4
J	13	2
QRS_m	0	0
(Q/R)	0	0
(R/S)	4	2
(Q/R)	0	0
Maximum QRS elevation	0	4
Maximum QRS azimuth	21	3

Normal limits are determined from the Veterans Administration data base of 510 cases recorded with electrodes at the fourth intercostal space level.

Table V Electrode distances in centimeters between V_4 and C in fourth and fifth intercostal spaces for 149 subjects

	Mean	*Range*
V to C, Fifth intercostal space	3.5	1 5-6 0
V to C Fourth intercostal space	5 3	3 0-7.5
C, Fifth intercostal space to C Fourth intercostal space	2.7	2 0-4.0

Table II Number of cases with significant amplitude changes using System 1 as reference

	System 2	*System 3*	*System 4*
Amplitude change† in R R or QRS_m	61 (41)*	104 (70)	101 (68)
R decrease	36 (24)	22 (15)	27 (18)
R increase	4 (3)	38 (26)	19 (13)
R decrease	5 (3)	25 (17)	16 (11)
R increase	39 (26)	46 (31)	61 (41)
QRS_m decrease	10 (7)	20 (13)	13 (9)
QRS_m increase	9 (6)	34 (23)	25 (17)
Amplitude change in T T or T_m	0	14 (9)	6 (4)
T decrease	0	2 (1)	1 (5)
T increase	0	2 (1)	1 (5)
T decrease	0	10 (7)	6 (4)
T increase	0	1 (5)	1 (5)
T_m decrease	0	1 (5)	0
T_m increase	0	7 (5)	3 (2)
No change in QRS or T amplitudes	82 (55)	34 (23)	35 (23)

Percentages of 149 subjects are shown in parentheses
†Amplitude change is calculated as the difference between an amplitude value in Systems 2 3 or 4 with respect to its value in System 1 The change is significant if it is both greater than 0 10 millivolt and at least 10 per cent of the value in System 1

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The data in Table II for R_x, R , and QRS_m were tested for significance of differences using the Wilcoxon matched pairs signed ranks test[12] This test is useful for making judgements about the magnitude and direction of differences within pairs Application of this test demonstrated that the trends for decreasing R_x and increasing R_z from Systems 1 to 2 were highly significant (p = 00003) On the other hand QRS_m changes were not significant, i e no trend toward increasing or decreasing magnitude was evident

When comparing Systems 1 to 3, the trend for R_x increase was also significant (p = 02) As noted from the p values, this trend was not so strong as the R_x decreasing trend for Systems 1 to 2 However, the total number of records for which R_x changes occurred was much greater for System 3 (60 opposed to 40) Trends for R and QRS_m increases were significant at p = 006 and p = 05 levels respectively, between Systems 1 and 3

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2 With all electrodes shifted from the fifth to the fourth interspace, R , R_z, and QRS_m changes occur in about 70 per cent of the cases, R_x is affected in about 40 per cent R in about 50 per cent, and QRS_m in about 35 per cent of the records In those records with changes R, R and QRS_m increase in about two thirds and decrease in about one third of the cases However as will be noted later in this section it is difficult to predict increases or decreases in amplitudes when electrode level is shifted from the fifth to the fourth interspace

In an effort to determine if electrocardiographic changes were correlated with disease groups

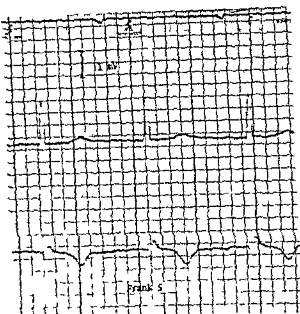


Fig 2A Frank lead recording with electrodes at the level of the fifth intercostal space Only x and z leads shown

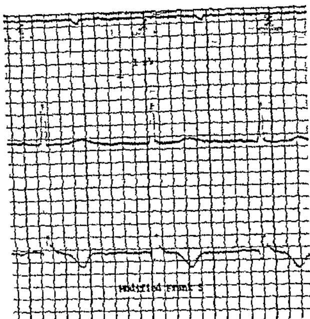


Fig 2B Frank lead recording of same patient with V substituted for C electrode *Note R increase from about 0 4 to 0 6 millivolt and R decrease from about 1 8 to 1 6 millivolt*

that the bipolar precordial leads can provide a lead vector almost parallel to the y axis when they are symmetrically located above and below the source (dipole) location [17] No quantitative figures were given for amplitude differences between the fourth and fifth intercostal space recordings

In the present study no attempt was made to determine which of the two electrode levels was optimum for the Frank lead system To do so would require ideally determination of the elec trical center of the heart There is an indirect relationship between the level of the electrical center and the level at which maximum QRS amplitudes are found In torso model experiments conducted by Frank [8] the critical horizontal level (maximum bulge in image space) usually corre sponded to this level for maximum QRS ampli tudes.

The differences in results between this study and that of Ritsema van Eck are *difficult* to reconcile but neither technique for estimating the critical horizontal level is sufficiently accurate for the determination of the optimum level in any specific case A final *resolution* of this question may not be possible for real subjects and, at the least will *require a study* using more exacting techniques

The results of the present study stand out in sharp contradiction to those reported recently by Riekkinen and Rautaharju [1] Using the same definitions for significant changes these authors *found that* R R and QRS_m *decreased* in 39 45 *and 40* per cent of their records (144 patients) when electrodes were shifted from the fifth to the fourth intercostal spaces in the supine position Increased values were found in less than 1 per cent of the records. These figures contrast sharply with results shown in Table II in which decreases in R_x R and QRS_m were observed in 15 17 and 13 per cent of the records and increases in 26 31, and 23 per cent of the records It is of interest to note that the percentages of records in which any changes occurred regardless of direction were remarkably similar for both studies

There may be at least one explanation for these discrepancies that is related to the subject's posi tion during electrode application In Table II of Riekkinen and Rautaharju [11] *data* are presented for electrocardiographic measurement changes with shift in electrode level *for both* supine and sitting subjects Although amplitudes decreased consistently in both *cases* when electrode level was shifted from the fifth to the fourth intercostal space the *percentages* of records in which this occurred was *considerably less* for the sitting subjects For example QRS_m decreased in 40 3 per cent for supine and in only 19 4 per cent *for sitting*

Table VI Number of cases having significant amplitude changes for 66 normal subjects 20 subjects with hypertensive cardiovascular disease (HCVD), and 9 subjects with pulmonary disease*

	System 2			*System 3*			*System 4*		
	Normals	*HCVD*	*Pulm dis*	*Normals*	*HCVD*	*Pulm dis*	*Normals*	*HCVD*	*Pulm. dis*
Amplitude changes —R R, or QRS_m	26 (39)†	6 (30)	4 (44)	48 (73)	13 (65)	5 (55)	49 (74)	13 (65)	4 (44)
R_x decrease	15 (23)	2 (10)	1 (11)	9 (14)	2 (10)	2 (22)	8 (12)	1 (5)	2 (22)
R increase	1 (2)	0	1 (11)	21 (32)	7 (35)	0	9 (14)	4 (70)	1 (11)
R decrease	2 (3)	0	1 (11)	5 (8)	1 (5)	3 (33)	7 (11)	1 (5)	2 (22)
R increase	9 (14)	3 (15)	1 (11)	23 (35)	7 (35)	1 (11)	26 (39)	8 (40)	1 (11)
QRS_m decrease	7 (11)	0	1 (11)	6 (9)	2 (10)	2 (22)	6 (9)	2 (10)	0
QRS_m increase	0	0	2 (22)	16 (24)	6 (30)	0	8 (12)	4 (20)	0
No change in QRS or T AMP	36 (55)	14 (70)	5 (55)	10 (15)	6 (30)	4 (44)	12 (18)	6 (30)	3 (33)

*See footnote to Table II for definition of significant changes
†Percentages are shown in parentheses

Table VII Number of records with significant changes for two studies in this laboratory (studies 1 and 2) and one reported by Riekkinen and Rautaharju (study 3)[19]

*Measurement**	*Study 1 (149 records)*	*Study 2 (137 records)*	*Study 3 (144 records)*
R			
4th ICS > 5th ICS	38	31	1
4th ICS = 5th ICS	89	68	87
4th ICS < 5th ICS	22	38	56
R			
4th ICS > 5th ICS	46	36	6
4th ICS = 5th ICS	78	60	73
4th ICS < 5th ICS	25	41	65
QRS_m			
4th ICS > 5th ICS	34	20	1
4th ICS = 5th ICS	95	78	85
4th ICS < 5th ICS	20	39	58

All recordings are for the supine position with electrodes in the fourth and fifth intercostal spaces (ICS)

Whether or not a particular record is misclassified obviously depends on a combination of measurement changes, which was not specifically determined in this study However, it seems clear that a change in diagnosis is likely to occur as a result of applying the same voltage level criteria to both fourth and fifth intercostal level recordings for the same subject

Figs 2 and 3 show the typical way in which lead voltages are affected by electrode position In Fig 2, lead voltages for the Frank fifth interspace level are compared when V_4 is used instead of C

Lead x is noticeably decreased and lead z increased in amplitude when using V_4 In Fig 3 fourth and fifth level Frank leads are compared For this patient, both x and z lead voltages are higher for the fifth interspace

In previous studies comparing fourth and fifth intercostal level recordings by Gau and Smith[13] (15 subjects) and by Slany[14] (50 patients), the authors found no statistical differences in Frank lead electrocardiographic amplitudes Our own findings are similar, but there is disagreement in the conclusions which were drawn Whereas Gau and Smith[13] conclude that a simple transformation could be used when comparing data in both electrode configurations individual variations found in our own study would not support this conclusion Furthermore as reported by Horan and associates[15] among others no general transformation can be applied to electrocardiograms to convert amplitudes or orientations from one system to another because of the wide range of biologic variations The conclusion by Slany[14] that results obtained with either electrode configuration were interchangeable is also inappropriate in view of the large amplitude differences detected in many individual cases e g, 70 per cent of records affected (Table II)

Ritsema van Eck,[16] in a study of electrode levels concluded that x and z lead electrodes should be located below the fourth intercostal space His conclusions were based on a cross correlation technique for determination of the optimum Frank electrode level in 44 normal subjects This technique relies on the assumption

Table VIII Comparison of means and ranges of amplitude changes among several studies For each subject the absolute value of the difference between the measurement in system 1 and that in systems 2 3 or 4 is determined The mean is then calculated for 149 subjects

	System 2 5th ICS–V		*System 3 4th ICS–C*		*System 4 4th ICS–V*		*Beat to Beat*†	*Day to Day normals*‡				*Day to Day abnormals*§	
								Mean		*96% Range*			
Measurement	*Mean*	*96% range*	*Mean*	*96% range*	*Mean*	*96% range*	*Mean + 2 S.D*	*m*	*unm*	*m*	*unm*	*Mean*	*96% range*
R	11	.3?	15	39	11	?6	08	09	14	.31	61	09	.36
R_s	10	41	14	.37	15	44	05	05	09	30	35	08	4?
QRS_m	08	25	15	37	12	37	08	.07	11	.21	.50	10	.35

All alues are in milli olts
†D ta are from Fischm n et al.
‡Data are from Willems et l.[?]
§Data are from Kim et al.[?]
Abbreviations ICS = intercostal sp ce S D = standard deviations m = marked unm = unmarked

Riekkinen and Rautaharju (their Table II) [?] The most striking features appear to be that (1) all three studies produce qualitatively different results and (2) the two studies from this laboratory are more nearly similar to each other than either is to the study of Riekkinen and Rautaharju[?] To test these suppositions further the complex chi square procedure was applied for each measurement to two groups at a time, e g study 1 versus study 2 study 1 versus study 3 and study 2 versus study 3 The null hypothesis used was that no difference exists between the pair of studies under test In fact for R and R the chi square value was not significant at the 0 05 level when comparing both studies from this laboratory Chi-square values were highly significant ($p < 0\ 0001$) when comparing either of these studies to that of Riekkinen and Rautaharju [?] For QRS_m the chi square value was borderline for $p = 0\ 05$ when comparing both studies from this laboratory Again when comparing either study with that of Riekkinen and Rautaharju[?] chi square values were highly significant with $p < 0\ 0001$ in both instances We must conclude then, that the data from both studies in this laboratory were not statistically dissimilar and that both sets of data were statistically different from those of Riekkinen and Rautaharju[?] It is apparent also from the data of Table VII that it generally is not possible to predict in which way amplitudes will change when electrode level is displaced from the fifth to the fourth intercostal space

It may be of interest to compare the variations in electrocardiographic measurements that were found in this study to those found in studies of beat to beat and day to day variations Fischmann and co workers[21] studied beat to beat and observer variation in a series of 58 Frank lead records They reported results for a variety of amplitude and duration measurements For R R and QRS_m they calculated values of 08 05 and 08 millivolts respectively representing mean differences plus two standard deviations of the differences using nine beats from each record These values are significantly lower than those obtained in this study (Table VIII)

Two of the recent studies on day to day variation of the Frank lead electrocardiogram were reported by Willems and co workers [?] for a series of 20 normal subjects and by Kim and co workers [?] for a series of 20 patients 19 of them with hypertensive cardiovascular disease Data from these studies for R R and QRS_m are also shown in Table VIII As a general observation it may be concluded from these data that variations caused by recording with Systems 2 3 or 4 as compared with System 1 are of the same order of magnitude as day to day variations This does not mean however that consistency with electrode locations in the Frank system is of little importance In the present study *no day to day* variations were included Thus the values shown in Table VIII reflect only those errors caused by intentionally displacing electrode locations If day to-day variations are considered in addition to this errors will most likely be compounded although they will not generally be additive algebraically

There appears to be no conclusive evidence for

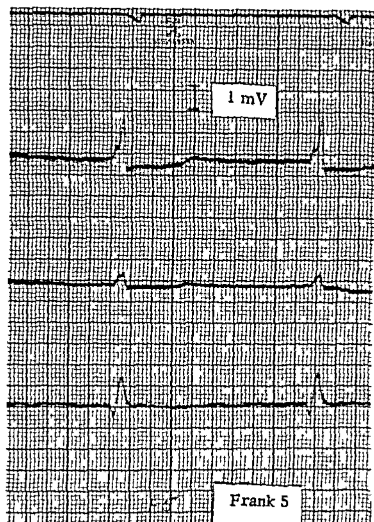


Fig 3A Frank lead recording with electrodes at the level of the fifth intercostal space

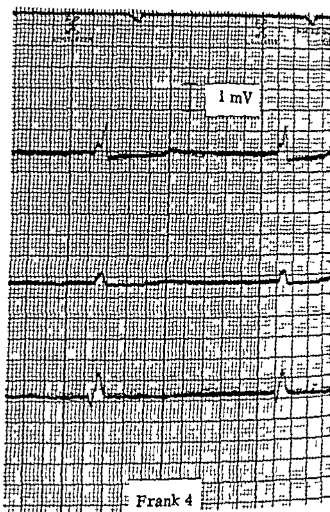


Fig 3B Frank lead recording of same patient with electrodes at the level of the fourth intercostal space Note R decrease from about 1 1 to 0 9 millivolt and R decrease from about 1 6 to 1 2 millivolt

subjects Since electrodes were not repositioned between supine and sitting positions, these differences in results were probably caused by skin shifts relative to the ribs

It is well known that the skin tends to shift upwards when an individual moves from standing or sitting to a supine position In locating a chest electrode at the level of the fifth interspace for a standing subject for example, experiences in our own laboratory have indicated that it will usually be at or closer to the fourth interspace with the subject supine In the study by Riekkinen and Rautaharju [19] fourth and fifth interspace electrode positions were marked with the subjects standing In the supine position these levels were probably closer to the third and fourth interspaces, in which case the reduced electrocardiographic amplitudes with the higher electrode levels are more understandable In the sitting position their results still are in contradiction, although slightly less so, to those in the present study in which electrode positions were marked with patients supine We can only surmise then that this difference in the subjects posture during marking of electrodes is responsible for the differences in results between the two studies There is, of course, also the possibility that these differences occurred by chance but the fact that a similar number of subjects was used in both studies makes this seem unlikely

Incidentally, the increase in electrocardiographic amplitudes noted by Riekkinen and Rautaharju[19] when subjects move from supine to sitting positions has also been observed in a recent study by Shapiro and colleagues [20] These authors have attributed this mainly to skin shifts (and thereby electrode shifts) relative to heart position

The discrepancies in results between those of Riekkinen and Rautaharju[19] and our own prompted a second study conducted in our laboratory with a new group of 137 male adults Table VII lists results of this study for R R, and QRS alongside results of the first study and those of

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the superiority of fifth or fourth intercostal levels for Frank lead recordings Nevertheless, there are persuasive reasons for electrocardiographers to agree on one choice or another Since 12 lead electrocardiograms continue to be most widely used, we should expect to find both kinds of recordings in demand for many years to come Perhaps the one important advantage for fifth over fourth intercostal levels is that shared elec trodes in a combination conventional/Frank lead patient cable are closer to the proper locations for conventional lead recordings

Conclusions

The findings in this study lead to these conclu sions

1 When considering a large inhomogeneous group of subjects differences in mean values of many commonly used amplitudes and orienta tions are not statistically significant among the four lead systems studied

2 Measurement changes for individual electro cardiograms occur frequently when V_4 is substi tuted for C, with R_x decreasing and R_z increasing in approximately 40 per cent of the records QRS_m was less often affected most likely because of the opposite changes occurring in R_x and R_z

3 When all electrodes are shifted upwards from the fifth to the fourth intercostal space for supine subjects about 70 per cent of the records were affected For any individual, it is not possible to predict which electrode level will result in higher electrocardiographic amplitudes

4 Electrocardiographic measurement changes caused by electrode level changes or substitution of V_4 for C are of the same order of magnitude as day to day variations

5 Analysis programs depending on individual amplitude measurements such as decision tree programs are likely to be considerably affected by electrode placement whether it be C alone or a complete level shift

6 Development of criteria for analysis pro grams should ideally be applied only to lead systems in which electrodes are located in the same manner

Summary

Frank lead electrocardiograms were recorded from 149 normal and abnormal adult males using four different electrode placements All chest electrodes were placed at (1) the fourth inter costal space level, (2) the fifth intercostal space level, (3) the fourth intercostal space level with V_4 substituted for C, and (4) the fifth intercostal space level with V_4 substituted for C

Differences in mean values of many commonly used amplitudes and orientations were not statis tically significant among the four recording meth ods but amplitude differences for individual subjects were often large and difficult to predict When V_4 is substituted for C, as commonly done in some laboratories R_x decreased and R_z increased by more than 10 per cent in about 40 per cent of the cases In about 70 per cent of the cases, R_x and R_z changed significantly when electrode level was shifted from the fifth to the fourth intercostal space For these 70 per cent it does not appear possible to accurately predict increase or decrease of R_x, R_z or QRS_m

Analysis programs which depend on individual amplitude measurements are likely to be signifi cantly affected by electrode placement It is suggested that criteria for analysis programs developed using a specified version of the Frank system should ideally be applied only to electro cardiograms recorded in the same manner

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9 Simonson E Horibe H Okamoto N and Schmitt O H Effect of electrode displacement on orthogonal leads,

Table I Atrial flutter data for patients injected with lidocaine over 20 seconds

Pt	Diagnosis	Weight (kg)	LIDO dose (mg)	Serum K (mEq/L)	Serum digoxin (ng/mL)	Other cardiac drugs: Drug	Dose (mg)	Hours before LIDO	Mean control AR (beats/min)	Lowest AR after LIDO (beats/min)	AR change after LIDO (beats/min)	Mean control VR (beats/min)	Mean VR 1-6 min after LIDO (beats/min)	Mean VR change after LIDO (beats/min)
1	CHD	104	100	4 6	none	Prop	20	5	294	268	−26	147	136	−11
2	CHD	83	100	5 6	undet		none		289	253	−36	138	132	−6
3	CHD	95	100	4 4	undet	QS	400	5	264	242	−22	132	123	−9
4	CMP	0	100	5 8	none		none		250	214	−36	62	55	−7
5	IDIO	47	75	4 4	none		none		298	270	−28	80	72	−8
6	CHD COPD	106	100	4 9	< 0 5	QG	324	4	280	266	−14	110	131	+21
7	CHD	84	100	4 0	1 73	QG	324	7	308	294	−14	154	146	−8
8	COPD	67	100	5 1	none		none		318	284	−34	158	147	−11
9	CHD	62	100	4 1	none		none		268	242	−26	93	120	+27
10	CHD	62	50	6 5	2.5		none		332	310	−22	88	93	+5
11	IDIO	70	100	4 2	none		none		264	244	−20	128	124	−4
12a	CMP	84	100	4 4	0 73		none		298	276	−22	148	138	−10
12b	CMP	76	100	4 8	1 87	QS	400	0 5	325	294	−31	101	148	+47
13	CMP	66	100	5 3	undet		none		288	262	−26	144	133	−11
14	MS	57	75	4 4	0 71		none		328	A Fib developed		91	92	+1
15	AS	75	100	3 3	0 79	QS	500	1.5	248	218	−30	94	91	−3
16	COPD CHD	69	100	4 8	none		none		316	298	−18	158	154	−4
Mean ± 1 SD									288 ±26	262 ±28	−26 ±7	119 ±31	120 ±29	+0 5 ±16

= $P < 0.001$

Abbreviations LIDO = lidocaine AR = atrial rate VR = ventricular rate CHD = coronary heart disease CMP = congestive cardiomyopathy IDIO = idiopathic COPD = chronic obstructive pulmonary disease MS = mitral stenosis AS = aortic stenosis undet = undetermined prop = propranolol QS = quinidine sulfate QG = quinidine gluconate A Fib = atrial fibrillation

with atrial flutter (patient No 12) received lidocaine injected over 20 seconds on two separate hospital admissions

Individual lidocaine doses are listed in Tables I to III Forty-eight of the 53 patients received a 100 mg dose of lidocaine One patient with atrial flutter (patient No 10) had received a lidocaine infusion which was stopped 90 minutes before the study He was given a 50 mg dose of lidocaine No other patient had received any lidocaine in the 24 hours prior to the study

Continuous electrocardiographic recording in a single lead (usually MCL1) was performed for 5 minutes prior to and at least 10 minutes following lidocaine injection utilizing a Birtcher Model 335 electrocardiograph at 25 mm/sec paper speed Blood pressure was recorded with a mercury sphygmomanometer In patients in whom lidocaine blood levels were determined samples were drawn through a 16 gauge Jelco needle which was placed in the antecubital vein of the arm opposite that used for lidocaine injection * Serum potassium levels and serum digoxin levels were determined from venous samples drawn immediately prior to the procedure Thirty seven patients were given lidocaine for therapeutic indications primarily for prophylactic use immediately prior to electrocardioversion Sixteen patients were given lidocaine for research reasons after informed consent was obtained There were no adverse effects in any patient given lidocaine for research purposes

Cardiac rates were determined by counting complexes on the continuous electrocardiographic write out A mean control rate for each patient was determined by counting the entire 5 minute period immediately before lidocaine injec

*Lidocaine levels were determined by Astra Pharmaceutical Products, Inc.

Lidocaine-induced cardiac rate changes in atrial fibrillation and atrial flutter*

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In the past 15 years lidocaine has become a very important drug for treating ventricular arrhythmias [1-4] Lidocaine is generally ineffective in treating supraventricular arrhythmias [4] This poor response of supraventricular arrhythmias may be explained by a much less prominent effect of lidocaine on action potentials and automaticity in atrial tissue as compared to His Purkinje fibers [5] Although lidocaine is rarely used to treat atrial arrhythmias situations commonly arise in which lidocaine is given for other indications in patients who have atrial arrhythmias as a coexisting disorder Most often, this involves treatment of beats presumed to be premature ventricular beats (PVBs) in patients with atrial flutter or atrial fibrillation The more widespread use of lidocaine as a routine prophylactic measure in patients with acute myocardial infarction[6,7] also entails administration of lidocaine to some patients with atrial flutter or atrial fibrillation

Isolated case reports have suggested that lidocaine may be a hazardous drug in patients with atrial flutter or atrial fibrillation with a rapid ventricular rate because of its potential to further increase ventricular rate [8-10] The significance of these reports remains uncertain even to experts in this field [11] and no warning has been issued with prescription information This problem has not been studied as regards incidence mechanism, predictability, or predisposing factors In the absence of adequate data policies regarding the use of lidocaine in the presence of atrial flutter or atrial fibrillation with rapid ventricular rates vary from tight restriction to unfettered use

In order to focus on the practical unanswered clinical questions we elected to study lidocaine as it is commonly used Thus we administered a standard 100 mg dose which was injected rapidly No attempt was made to eliminate other concomitantly used cardiac medications since an interaction of lidocaine with other drugs needed to be considered

Materials and methods

Eighteen patients with atrial flutter and 35 patients with atrial fibrillation were studied The mean age of all patients was 62 years with a range from 42 to 85 years In all patients 2 per cent lidocaine hydrochloride* was injected into a vein in the antecubital or forearm area through a short segment of connecting tubing In 16 of the patients with atrial flutter and in all 35 patients with atrial fibrillation the lidocaine was injected over 20 seconds Three patients with atrial flutter received lidocaine injected over a 4 minute period or longer One of these three patients (patient No 4) had received the same dose of lidocaine injected over 20 seconds 2 days previously One patient

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*Xylocaine Astra Pharmaceutical Worcester Mass.

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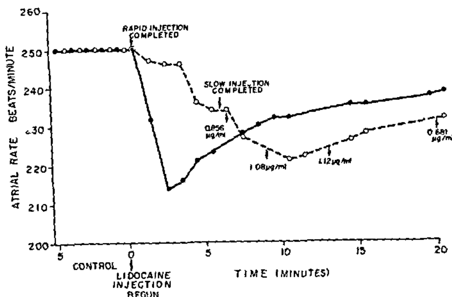


Fig 2 Atrial rate before and after lidocaine in atrial flutter patient No 4 This patient initially received 100 mg. of lidocaine injected over 20 seconds (*solid line*) Two days later he received 100 mg of lidocaine injected over 6 minutes (*broken line*) Blood lidocaine levels were measured following the slow injection and are indicated along the curve at the time they were drawn

Table II Atrial flutter data for patients injected with lidocaine over 4 minutes or longer

Pt	Diagnosis	Weight (Kg)	LIDO dose (mg)	Serum K mEq/L	Serum digoxin (ng/ml)	Other cardiac drugs within 8 hours	Mean control AR (beats/min)	Lowest AR after LIDO (beats/min)	AR change after LIDO (beats/min)	Mean control VR (beats/min)	Mean VR 1 6 min after LIDO (beats/min)	Mean VR change after LIDO (beats/min)
4†	CMP	0	100	5 3	none	none	50	2?1	−29	62	58	−4
17‡	CMP	5?	100	4 3	0.5	none	3?8	303	−25	78	78	0
18‡	IDIO	93	100	4.2	0 88	none	244	2 8	−16	126	117	−9
Mean							?74	?51	−23	89	84	−4
± 1 SD							±47	±46	±7	±33	±30	±5

P = < 0 001
† = Lidocain injected over 6 minutes
‡ = Lidocain injected over 4 minutes
Abbreviations LIDO = lidocaine AR = atrial rate VR = ventricular rate IDIO = id pathic

lidocaine (P < 0 001) In 15 of 16 atrial fibrillation patients (94 per cent) with statistically significant ventricular rate changes the change in ventricular rate occurred abruptly within 1 minute of lidocaine injection

In two patients with atrial fibrillation lidocaine induced ventricular rate increases were associated with potentially serious clinical events Fig 3 shows ECG rhythm strips before and after lidocaine in patient No 4 The lidocaine was given prior to an electrocardioversion One minute after the lidocaine was given the ventricular rate accelerated by 30 beats/minute By 4 minutes after lidocaine the ventricular rate had increased by 40 to 50 beats/minute from the control rate and frequent long runs of wide QRS beats with a left bundle branch block configuration were seen The cycle lengths initiating and terminating all of these salvos of wide beats were consistent with aberration in the left bundle branch The ventric

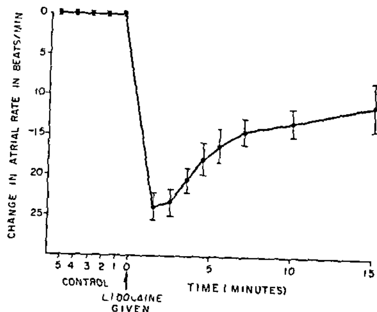


Fig 1 Mean change in atrial rate ±1 S E M in the 16 patients with atrial flutter receiving rapid injection of lidocaine

tion A mean rate for each patient after lidocaine injection was determined by counting the entire 5 minute period from 1 to 6 minutes after lidocaine injection Ventricular rates were counted in patients with atrial fibrillation while both atrial and ventricular rates were counted in patients with atrial flutter

The statistical significance of any rate change in each individual patient was determined by using Student's t test The 5 minute time period immediately before and the 1 to 6 minute time period after lidocaine injection were each divided into ten 30 second segments for this analysis The statistical significance of changes for the entire group of patients with atrial flutter and the group with atrial fibrillation were determined using Student's t test for correlated means Correlation coefficients were calculated using Pearson's product moment For calculations of correlation coefficients serum digoxin levels reported by the laboratory as < 0 5 ng /ml were considered to be 0 25 ng /ml Patients who were receiving digoxin but in whom serum levels were not determined (marked undet in Tables I to III) were excluded from these calculations

Results

Table I shows the clinical data and response to lidocaine in the 16 patients with atrial flutter given lidocaine over 20 seconds Patient No 14 developed transient atrial fibrillation following lidocaine injection The other 15 patients all showed a prompt decrease in atrial rate after lidocaine The peak decrease in atrial rate occurred 1 to 2 minutes after lidocaine injection with a gradual return towards the control atrial rate over the next 10 to 20 minutes of recording (Fig 1)

Table II indicates patients No 17 and 18 were given lidocaine over 4 minutes rather than over 20 seconds Patient No 4 received 100 mg of lidocaine injected over 20 seconds one day and 100 mg of lidocaine injected over 6 minutes 2 days later (Table II and Fig 2) These three patients showed slowing of the atrial rate similar to that observed in patients with lidocaine injected over 20 seconds

This consistent decrease in atrial rate after lidocaine was accompanied by a variable and unpredictable change in ventricular rate The ventricular rate for the entire group of patients with atrial flutter and rapid lidocaine injection was unchanged after the lidocaine injection However three individual patients (patients No 6 9 and 12) significantly increased their ventricular rate ($P < 0.001$) after lidocaine The mean rate increases in these three patients during the period from 1 to 6 minutes after lidocaine were 21 27, and 47 beats/minute respectively

In seven patients the ventricular rate decreased significantly ($P < 0.001$) after lidocaine The patients with a fall in ventricular rate generally had no change in A V conduction Thus slowing of the atrial rate was accompanied by slowing of the ventricular rate In patients No 6 9, and 12 as the atrial rate slowed the A V conduction ratio decreased and the ventricular rate increased The atrial flutter rate changes and significant ventricular rate changes occurred abruptly with 1 minute of lidocaine injection

Table III shows the clinical data and response to lidocaine of the patients with atrial fibrillation Considering the group as a whole the ventricular rate increased 6 beats/minute following lidocaine ($P < 0.01$) The ventricular rate increase in some individual patients was much greater and was clinically relevant In 14 individual patients the ventricular rate increased significantly after lidocaine as compared to the control period immediately prior to lidocaine injection ($P < 0.005$) In three of these patients the rate increase was greater than 20 beats/minute In two patients the ventricular rate significantly decreased after

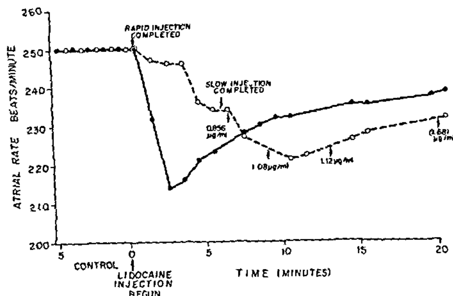


Fig 2 Atrial rate before and after lidocaine in atrial flutter patient No 4 This patient initially received 100 mg of lidocaine injected over 20 seconds (*solid line*) Two days later he received 100 mg of lidocaine injected over 6 minutes (*broken line*) Blood lidocaine levels were measured following the slow injection and are indicated along the curve at the time they were drawn

Table II Atrial flutter data for patients injected with lidocaine over 4 minutes or longer

Pt	Diagnosis	Weight (kg)	LIDO dose (mg)	Serum K mEq/L	Serum digoxin (ng/ml)	Other cardiac drugs within 8 hours	Mean control AR (beats/min)	Lowest AR after LIDO (beats/min)	AR change after LIDO (beats/min)	Mean control VR (beats/min)	Mean VR 1-6 min after LIDO (beats/min)	Mean VR change after LIDO (beats/min)
4†	CMP	70	100	5 3	none	none	250	221	−29	62	58	−4
17‡	CMP	5?	100	4 3	0 5	none	3?8	303	−25	78	78	0
18‡	IDIO	93	100	4 2	0 88	none	244	228	−16	126	117	−9
Mean							274	251	−23	89	84	−4
± 1 SD							±47	±46	±7	±33	±30	±5

P = < 0 001

† = Lidocaine injected over 6 minutes

‡ = Lidocaine injected over 4 minutes

Abbreviations LIDO = lidocaine AR = atrial rate VR = ventricular rate IDIO = idiopathic

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Table III Atrial fibrillation data

Pt	Diagnosis	Weight (Kg)	LIDO dose (mg)	Serum K (mEq /L)	Serum digoxin (ng /ml)	Other cardiac drugs			Mean control VR (beats/min)	Mean VR 1 6 min after LIDO (beats/min)	Mean VR change after LIDO (beats/min)
						Drug	Dose (mg)	Hours before LIDO			
1	CHD	73	110	4 2	none	QS	400	4	113	100	−13
2	CHD CHF	71	100		undet	QS	200	6	98	92	−6
3	IDIO	86	100	4 5	none		none		81	91	+10
4	CHD	92	100	4 4	0 71	QS	200	2 5	142	176	+34
5	AI	85	100	4 5	none		none		53	58	+5
6	AS COPD	58	100	4 4	3 7		none		113	115	+2
7	IDIO	134	125	5 0	0 85		none		109	120	+11†
8	CHD	125	125	4 3	<0 5	QG	324	4	101	116	+15
9	IDIO	100	100	4 3	<0 5	QG	324	3 5	86	93	+7
10	CHD	55	100	5 4	0 80		none		93	101	+8
11	CHD CHF	90	100	4 8	1 7	QG	324	5	98	103	+5
12	MS	74	100	3 8	undet	QG	324	4	95	110	+15
13	COPD CHD	64	100	5 1	undet		none		171	181	+10†
14	HT	53	100	3 6	none		none		88	90	+2
15	MS	72	100	3 8	<0 5	QG	324	5	142	142	0
16	HT	72	100		undet	PROP	20	6	140	136	−4
17	CHD	62	100	4 6	1 45		none		118	105	−13
18	IDIO PC	82	100	3 4	<0 5		none		140	140	0
19	IHSS	100	100	4 0	none	QS	300	1	91	106	+15
20	COPD MS	59	100	3 7	1 95		none		85	89	+4
21	MS	66	100	4 1	74		none		65	71	+6
22	CHD AS	67	100	4 4	1 51	QS	300	4 5	86	95	+9†
23	CHD	85	100	4 5	2 25	QG	324	4	123	129	+6
24	CMP	75	100	3 8	1 85		none		72	73	+1
25	CHD COPD	84	100	4 7	1 15		none		106	103	−3
26	COPD	88	100	4 1	2 13		none		136	136	0
27	CHD	82	100	3 6	1 15		none		69	64	−5
28	CMP	77	100	4 6	1 00		none		119	128	+9
29	CHD CHF COPD	68	100	3 5	undet		none		122	117	−5
30	CHD COPD	67	100	2 7	2 6		none		74	75	+1
31	IDIO	93	100	5 0	undet	QG	324	6	92	102	+10
32	MS CHD	70	100	5 0	1 00	QS	400	1	78	83	+5
33	CMP	56	100	4 5	<0 5	QS	300	3 5	108	133	+25
34	CMP	88	100	3 7	<0 5	QS	300	4	74	98	+24
35	CHD COPD	71	100	4 2	0 88		none		93	102	+9
Mean									102	108	+6
± 1 SD									±26	±28	±10

= P < 0 001
† = P < 0 005
Abbreviations LIDO = lidocaine VR = ventricular rate COPD = chronic obstructive pulmonary disease MS = mitral stenosis CHD = coronary heart disease AS = aortic stenosis CMP = congestive cardiomyopathy IDIO = idiopathic CHF = congestive heart failure AI = aortic insufficiency HT = hypertension PC = pericarditis IHSS = idiopathic hypertrophic subaortic stenosis undet = undetermined QS = quinidine sulfate QG = quinidine gluconate PROP = propranolol

ular rate increase and long runs of aberrant beats (many lasting 30 seconds or more) persisted for 17 minutes at which time the elective cardioversion was successfully performed without difficulty The patient had no symptoms and no change in blood pressure during this period of ventricular rate increase A serum lidocaine level drawn 8 minutes after the lidocaine injection, in the midportion of the period of ventricular acceleration, was 1 47 μg/ml (lidocaine base)

Patient No 13 in Table III was hospitalized because of marked dyspnea with a history of severe chronic obstructive lung disease He was found to be in atrial fibrillation with a ventricular rate of 170 beats/minute The patient had been taking digoxin 0 5 mg daily His serum digoxin

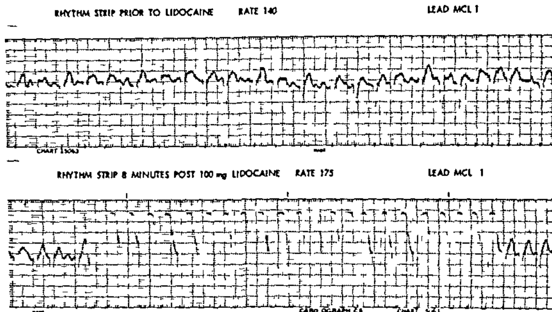


Fig 3 Electrocardiographic rhythm strips before and after lidocaine injection in atrial fibrillation patient No. 4

and K levels were unknown at that time It was elected to cardiovert the patient and 100 mg of lidocaine were given over 20 seconds as a prophylactic measure prior to the cardioversion One minute after the lidocaine was given the ventricular rate increased to between 180 and 190 beats/minute The blood pressure which had been 110/70 was then unobtainable and the patient appeared confused and diaphoretic The patient was cardioverted to normal sinus rhythm and recovered The adverse effect seems clearly related to lidocaine but it is uncertain whether the primary effect was ventricular rate acceleration or hemodynamic depression followed by a secondary ventricular rate increase This was the only patient in whom a fall in blood pressure occurred after lidocaine injection

Serial lidocaine blood levels were determined in a small representative sample of patients to document the range of blood levels obtained with this method of administration Fig 4 demonstrates therapeutic blood levels during the time of lidocaine induced atrial and ventricular rate changes The curve for lidocaine blood levels closely mirrors the curve for atrial rate decrease after lidocaine (Fig 1)

Baseline atrial and ventricular rates serum potassium levels serum digoxin levels and lidocaine dose/kg of body weight were not useful in predicting either atrial or ventricular rate changes after lidocaine The only significant correlation was between the serum digoxin level and the degree of ventricular rate change after lidocaine in atrial fibrillation patients ($r = -0.38$ $P < 0.05$)

Quinidine did have an important influence on ventricular rate changes Nine of 15 atrial fibrillation patients (60 per cent) who were also receiving quinidine significantly increased their ventricular rate after lidocaine while only five of 20 atrial fibrillation patients (25 per cent) who were not receiving quinidine significantly increased their ventricular rate ($P < 0.01$) Two of three atrial flutter patients and three of three atrial fibrillation patients whose ventricular rate increased by more than 20 beats/minute were receiving quinidine

Discussion

These data help clarify the response to lidocaine in patients with atrial flutter and atrial fibrillation Atrial flutter rates show an immediate and consistent fall when lidocaine is administered This might be explained by lidocaine s ability to decrease conduction velocity in atrial tissue The atrial slowing occurred whether the lidocaine was injected slowly over several minutes or was injected rapidly over 20 seconds (a method of administration which results in transiently toxic arterial lidocaine levels)[13] Fig 2 demon

Table III Atrial fibrillation data

Pt	Diagnosis	Weight (kg)	LIDO dose (mg)	Serum K (mEq/L)	Serum digoxin (ng/ml)	Other cardiac drugs: Drug	Other cardiac drugs: Dose (mg)	Other cardiac drugs: Hours before LIDO	Mean control VR (beats/min)	Mean VR 1 6 min after LIDO (beats/min)	Mean VR change after LIDO (beats/min)
1	CHD	73	110	4 2	none	QS	400	4	113	100	−13
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3	IDIO	86	100	4 5	none		none		81	91	+10
4	CHD	92	100	4 4	0 71	QS	200	2 5	142	176	+34
5	AI	85	100	4 5	none		none		53	58	+5
6	AS COPD	58	100	4 4	3 7		none		113	115	+2
7	IDIO	134	125	5 0	0 85		none		109	120	+11†
8	CHD	125	125	4 3	<0 5	QG	324	4	101	116	+15
9	IDIO	100	100	4 3	<0 5	QG	324	3 5	86	93	+[illegible]
10	CHD	55	100	5 4	0 80		none		93	101	+8
11	CHD CHF	90	100	4 8	1 7	QG	324	5	98	103	+5
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13	COPD CHD	64	100	5 1	undet		none		171	181	+10†
14	HT	53	100	3 6	none		none		88	90	+2
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17	CHD	62	100	4 6	1 45		none		118	105	−13
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19	IHSS	100	100	4 0	none	QS	300	1	91	106	+15
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21	MS	66	100	4 1	74		none		65	71	+6
22	CHD,AS	67	100	4 4	1 51	QS	300	4 5	86	95	+9†
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25	CHD COPD	84	100	4 7	1 15		none		106	103	−3
26	COPD	88	100	4 1	2 13		none		136	136	0
27	CHD	82	100	3 6	1 15		none		69	64	−5
28	CMP	77	100	4 6	1 00		none		119	128	+9
29	CHD CHF COPD	68	100	3 5	undet		none		122	117	−5
30	CHD COPD	67	100	2 7	2 6		none		74	75	+1
31	IDIO	93	100	5 0	undet	QG	324	6	92	102	+10
32	MS CHD	70	100	5 0	1 00	QS	400	1	78	83	+5
33	CMP	56	100	4 5	<0 5	QS	300	3 5	108	133	+25
34	CMP	88	100	3 7	<0 5	QS	300	4	74	98	+24
35	CHD COPD	71	100	4 2	0 88		none		93	102	+9
Mean ± 1 SD									102 ± 26	108 ± 28	+6 ± 10

= $P < 0\ 001$
† = $P < 0\ 005$
Abbreviations LIDO = lidocaine VR = ventricular rate COPD = chronic obstructive pulmonary disease MS = mitral stenosis CHD = coronary heart disease AS = aortic stenosis CMP = congestive cardiomyopathy IDIO = idiopathic CHF = congestive heart failure AI = aortic insufficiency HT = hypertension PC = pericarditis IHSS = idiopathic hypertrophic subaortic stenosis undet = undetermined QS = quinidine sulfate QG = quinidine gluconate PROP = propranolol

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Patient No 13 in Table III was hospitalized because of marked dyspnea with a history of severe chronic obstructive lung disease He was found to be in atrial fibrillation with a ventricular rate of 170 beats/minute The patient had been taking digoxin 0 5 mg daily His serum digoxin

terms of reported cases is greatest in atrial flutter Lidocaine should be used with great caution if at all in patients with atrial flutter and 2 1 A V response

The second problem lidocaine may create when used in atrial fibrillation or flutter with a rapid ventricular rate is that of aberrant conduction Wide QRS beats presumed to be PVBs are the usual reason for giving lidocaine to patients with atrial tachyarrhythmias A clear distinction between ventricular ectopy and aberrant conduction of supraventricular impulses may be very difficult in such patients Lidocaine may accelerate the ventricular rate and aggravate the problem of aberrant conduction (Fig 3) The depressant effect of lidocaine on ventricular conduction tissue may also contribute to aberration particularly in patients with underlying fascicular conduction disease given rapid bolus injections

We share Marriott and Bieza s abhorrence of the lidocaine reflex when faced with atrial fibrillation or flutter a rapid ventricular rate and frequent wide QRS complexes Measures to slow the ventricular rate are often the most appropriate therapy However since a precise diagnosis may not be possible without His bundle recordings and since alternative methods of treatment may also be hazardous we believe lidocaine does have a role in some of these circumstances if used with discrimination

The data presented here demonstrate that clinically significant ventricular acceleration in patients with atrial flutter or atrial fibrillation who are given lidocaine is not a rare phenomenon In the presence of quinidine it is a very common phenomenon Lidocaine should be used with caution in the presence of atrial arrhythmias with an already rapid ventricular rate

Summary

To assess atrial and ventricular rate changes after lidocaine injection 18 atrial flutter patients and 35 atrial fibrillation patients were given intravenous lidocaine mean dose 100 mg Continuous electrocardiographic recording for 5 minutes before and at least 10 minutes after lidocaine injection was used to determine rate changes The atrial flutter rate decreased after lidocaine in 17 of 18 patients (94 per cent) mean maximal decrease 27 beats/minute The ventricular rate response in atrial flutter was variable but in three patients increased 21 27 and 47 beats/minute respectively ($P < 0\,001$) In atrial fibrillation the mean ventricular rate after rapid lidocaine injection increased six beats/minute ($P < 0\,01$) In three of 35 atrial fibrillation patients (9 per cent) the ventricular rate increase was greater than 20 beats/minute ($P < 0\,001$) and in two patients (6 per cent) the ventricular rate increase was associated with potentially serious clinical events Lidocaine induced ventricular rate increases are common in atrial flutter and fibrillation particularly in patients who are also receiving quinidine

The authors wish to express their appreciation to M B Meyer M D Astra Pharmaceutical Products Inc for performing the lidocaine blood levels

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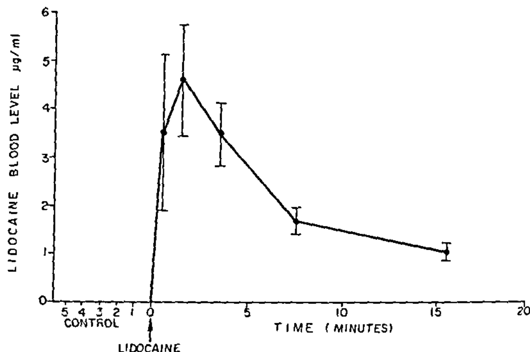


Fig 4 Mean lidocaine base levels ±1 S E M before and after rapid lidocaine injection in five representative patients (atrial fibrillation patients No 18 and 25 and atrial flutter patients No 5 8 and 12a)

strates that atrial slowing was present when lidocaine blood levels were in the low therapeutic range

The two previous case reports of serious ventricular acceleration after lidocaine administration in patients with atrial flutter also demonstrated atrial slowing[8, 9] Slowing of the atrial flutter rate with lidocaine may be an important factor affecting the more clinically crucial ventricular rate response A decrease in the number of impulses reaching the A V node may result in a greater number of impulses per minute conducted to the ventricles

Another very important consideration regarding lidocaine induced ventricular rate changes is the effect of lidocaine on A V conduction velocity and refractory periods Changes could result either from direct effects of lidocaine on the A V node or from alterations in the autonomic state A V conduction and refractory periods cannot be measured by standard techniques in the presence of atrial flutter or atrial fibrillation Previous studies reported in patients with sinus rhythm have shown no consistent effect of lidocaine on A V node refractoriness or conduction although a shortening of the effective refractory period was noted in a few patients[13, 14] These parameters have not been measured when quinidine is also present, a factor which seems quite relevant in light of our data Further studies are necessary to evaluate this interaction between lidocaine and quinidine

It had been anticipated that serum potassium levels and serum digoxin levels would be important in influencing lidocaine's effects on cardiac rates Lidocaine's depressant effect on cardiac conduction tissue has been shown to increase with increasing potassium concentrations[12] while dogoxin has clinically important effects on the A V node which slow the ventricular rate in atrial flutter and in atrial fibrillation In contrast to the clear interaction from quinidine there was no significant influence from serum potassium levels and only a weak negative correlation of serum digoxin levels with ventricular rate changes The most dramatic ventricular acceleration (atrial flutter patient No 12b) occurred with a serum digoxin level of 1 84 ng/ml Thus digoxin affords incomplete protection against ventricular rate increases in patients with atrial flutter or atrial fibrillation who are given lidocaine

Ventricular rate increases after lidocaine in patients with either atrial flutter or atrial fibrillation are most likely to cause problems when the ventricular rate is already rapid Clinical problems may develop from either of two mechanisms

First of all the rate increase itself may be marked enough to seriously impair cardiac output This danger both theoretically and in

Cholelithiasis A frequent complication of artificial heart valve replacement

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A mild usually well compensated intravascular hemolytic process has been described in patients with valvular heart disease [1-3] especially when the aortic valve is severely damaged [4,5] Numerous studies [5-9] have demonstrated a greater yet still mild degree of hemolysis associated with various types of normally functioning valve prostheses The hemolytic process can become severe and inadequately compensated when ball variance [11-13] or paraprosthetic leaks develop

A report by Merendino and Manhas [7] in June 1973 implicated valve prostheses with the development of gallstones In 1968 Glenn and Redo reported an increased prevalence of gallstones in women with mitral valve disease With this limited evidence that mild mechanical hemolysis is not as innocuous as considered previously a study was undertaken to determine the prevalence of gallstones in prosthetic valve recipients followed in the Los Angeles County–USC Medical Center (LAC–USC–MC) outpatient clinic For comparative purposes a survey of autopsied cases was also undertaken to determine the prevalence of gallstones in patients with rheumatic and/or other forms of severe valvular heart disease

Methods

Our study group (Group A) consists of 46 valve prosthesis patients who attended our clinic at LAC–USC–MC and had survived valve replacement for 18 months or longer Sixteen had Smeloff Cutter aortic valves two had Bjork Shiley aortic valves three had Starr Edwards aortic valves eighteen had Kay Shiley mitral valves three had Starr Edwards mitral valves and four had two implanted prostheses of the Smeloff Cutter and/or Kay Shiley type This group of patients represented three ethnic groups and ages that ranged from 20 to 69 years All of the patients had normally functioning prosthetic valves and there was no evidence to indicate the presence of ball or poppet variance or paraprosthetic leaks

An oral cholecystogram was performed in each of these patients to determine the presence or absence of gallstones A standard dose of iopanoic acid USP (Telepaque) was utilized when required a double dose was employed for better visualization of the gallbladder The presence of a mild hemolytic process was established in nearly all cases utilizing one or more of the following determinations serum haptoglobin lactic dehydrogenase total and direct acting bilirubin serial reticulocyte counts serial hematocrits and urine examination for hemosiderin

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Table I Comparison of prevalence of gallstones in the heart valve prosthesis recipients (Group A) rheumatic heart disease cases (Group B), and severe valvular heart disease cases (Group C)

Age Intervals	*Group A*	*Group B*	*Group C*	*Results of statistical tests for difference*	
				Between B & C	*Between A & B*
20-29	0/ 2 = 0 0%	4/54 = 7 4%	1/ 6 = 16 7%	–	–
30 39	3/13 = 23 1%	11/143 = 7 7%	3/24 = 12 5%	NS	NS
40-49	4/ 9 = 44 4%	21/232 = 9 1%	3/22 = 13 6%	NS	••
50-59	9/17 = 52 9%	39/363 = 10 7%	3/28 = 10 7%	NS	•
60 69	2/ 5 = 40 0%	78/474 = 16 5%	0/ 7 = 0 0%	–	–
Total	18/46 = 39 1%	153/1266 = 12 1%	10/87 = 11 5%	NS	•
Sex					
Male	7/19 = 36 8%	60/683 = 8 8%	2/50 = 4 0%	NS	•
Female	11/27 = 40 7%	93/583 = 16 0%	8/37 = 21 6%	NS	••
Ethnic Groups					
Caucasian	7/18 = 38 9%	110/914 = 12 0%	7/59 = 11 9%	NS	••
Negro	3/10 = 30 0%	16/179 = 8 9%	0/9 = 0 0%	–	
Spanish American	8/18 = 44 4%	27/173 = 15 6%	3/19 = 15 8%	NS	••

Note —denotes inadequate sample sizes for statistical tests NS denotes non significance
denotes significance at the 0 01 level
denotes significance at the 0 05 level

The autopsy results of two other groups of patients were evaluated Group B consisted of 1,266 rheumatic heart disease cases autopsied at LAC–USC–MC between 1949 and 1973 Group C was a subset of Group B and consisted of 87 patients with severe valvular heart disease who had required surgical repair and/or valve replacement but did not survive valve replacement for a period greater than one month The presence or absence of gallstones was determined in both groups and correlated with their age sex and race The 87 cases in Group C were studied in greater detail to determine the valve(s) that were predominantly affected by the disease process because turbulence often has been cited as a factor leading to intravascular hemolysis Group C was selected for analysis because the degree of turbulence associated with the affected valves of that group probably was less than occurred in Group A but greater than occurred in Group B

The prevalence of gallstones was determined in all three groups and was correlated with age sex, race and the valve site involved

Results

A diagnosis of rheumatic heart disease was established at autopsy in 2 046 of 46 041 cases surveyed The prevalence of rheumatic heart disease was 44 4 per 1 000 autopsied cases Cholelithiasis was present in 301 cases or 14 7 per cent of all rheumatic heart disease cases autopsied here Patients in ethnic groups other than Caucasian Negro, and Spanish American and those outside the age range 20 to 69 years subsequently were eliminated from the 2 046 rheumatic heart disease cases in order to make direct comparisons with Groups C and A As a result, 1 266 rheumatic heart disease cases (Group B) were eligible for statistical comparison of prevalence of gall stones

Group A—Heart valve prostheses recipients Table I presents information on prevalence of gallstones for the 46 heart valve prostheses recipients in our study for comparison with the Group B and C results Although the prevalence of gallstones appeared to show a similar progressive increase with age and similar differences between males and females and among ethnic groups, no statistically significant differences were found with respect to age sex and race within this group This is due largely to the relatively small sample of patients in our study In general, the over all prevalence of gallstones in our group of heart valve prostheses recipients is 39 1 per cent which is much higher than either Group B or Group C

Group B—Rheumatic heart disease group Cholelithiasis was present in 153 of the 1 266 cases

(12.1 per cent) in this group. Table I presents the progressive increase in prevalence of gallstones with advancing age as well as the difference between males and females and ethnic groups. The progressive increase of gallstone prevalence with advancing age and the higher prevalence in females were found to be statistically significant at the 0.01 level. Although the prevalence rate appeared higher in the Spanish American group and was lower in the Negro group, the prevalence rates among ethnic groups were not found to be statistically significant.

Group C—Severe valvular heart disease group. All 87 autopsied cases with severe valvular heart disease were eligible for comparison with the study group with respect to age and ethnicity. However, the numbers of patients in the age intervals of 20 to 29 years and 60 to 69 years and in the Negro group were relatively small so that comparisons for those age and race classifications were thereby restricted. In this group of 87 selected cases with severe valvular heart disease ten (11.5 per cent) had cholelithiasis. Table I presents the distributions of the prevalence of gallstones in Group C by age, sex, and race. The differences in prevalence of gallstones among the various age groups and among the three ethnic groups were not found to be statistically significant within this group but the difference between males and females was significant at the 0.05 level. Due to differences in the distributions of age, sex, and race between this group and Group B, comparisons between them should be made for each classification rather than the entire group as a whole. However, there was no statistically significant difference between Groups B and C in any classification (Table I, *second column from the right*).

The patients were screened in an outpatient setting for evidence suggestive of hemolysis. All patients were at least three months post operation at the time of the screening. Either a positive urine examination for hemosiderin or a serum haptoglobin of less than 50 mg./ml. was found in 41 of the 44 patients (93 per cent) in whom data was available. Random corrected reticulocyte counts were obtained on multiple occasions in 45 patients and were averaged for each patient. The mean corrected reticulocyte count for the total group was 1.95 ± 0.79. The mean for the 18 patients with gallstones (2.19 ± 1.02) was higher than those without gallstones (1.81 ± 0.58), but a t test comparison did not reveal a statistically significant difference. Although a mild degree of hemolysis was felt to be present, significant anemia was not a problem in our patient population. The mean hemoglobin for the male patients was 15.11 ± 1.39 Gm./100 ml. and for the female patients was 13.55 ± 1.57 Gm./100 ml. Only three patients had hemoglobins outside of the normal range; none had a hemoglobin of less than 9 Gm./100 ml. and other etiologies for the anemia were present.

Comparisons of prevalence of gallstones were made among the three groups of patients with respect to each classification of age, sex, and race. The prevalence rates as well as the statistical test findings are presented in Table I; note that the over-all prevalence of gallstones in Group B is very close to that of Group C. No significant differences in prevalence of gallstones were found between the rheumatic heart disease patients and the severe valvular heart disease subset. With the exception of the age interval 20 to 29 years, the heart valve prostheses recipients were found to have higher prevalence rates than both the rheumatic heart disease group (Group B) and the severe valvular disease group (Group C). Between ages 40 to 49 years, the prevalence rate is about four times higher in the valve protheses recipients (44.4 per cent compared to 9.1 per cent and 13.6 per cent) and between ages 50 to 59 years it is about five times higher (52.9 per cent compared to 10.7 per cent and 10.7 per cent). The prevalence is almost doubled for females (40.7 per cent compared to 16.0 per cent and 21.6 per cent) and is about four times higher for males (36.8 per cent compared to 8.8 per cent and 4.0 per cent). In all ethnic groups, the over-all prevalence of gallstones is about three times greater in the group of valve prostheses recipients.

Our present data enable an exploratory comparison to be made of the prevalence of gallstones with respect to the valve site involved. Table II indicates the prevalence rates for males and females with respect to the valve sites involved for the severe valvular heart patients (Group C) and the heart valve prostheses recipients (Group A). Note that when multiple valves were severely damaged the lesion was described as being combined. It appears that the prevalence of gallstones in valve recipients (Group A) is higher in the group involving the mitral valve than in the aortic valve group. This

Table II Exploratory comparisons of prevalence of gallstones between valve prosthesis recipients (Group A) and severe valvular heart disease patients (Group C) with respect to valve site and sex

Male			*Female*		
Involved valve site	*Group A*	*Group C*	*Involved valve site*	*Group A*	*Group C*
Aortic	5/14 = 35 7%	1/21 = 4 8%	Aortic	2/7 = 28 6%	0/6 = 0 0%
Mitral	2/4 = 50 0%	0/20 = 0 0%	Mitral	7/17 = 41 2%	6/25 = 24 0%
Combined	0/1 = 0 0%	1/9 = 11 1%	Combined	2/3 = 66 7%	2/6 = 33 3%

Table III Male/female ratios in various patient groups with and without prosthetic heart valve replacement and comparisons with the literature

Group	Reference	*Total No patients*			*No with gallstones*			*Per cent with gallstones*		
		Male	*Female*	*Ratio*	*Male*	*Female*	*Ratio*	*Male*	*Female*	*Ratio*
General autopsy	Newman and Northup	26 479	17 838	1 48	1 914	2 820	0 68	7 2	15 8	0 46
B	This study	683	583	1 17	60	93	0 65	8 8	16 0	0 55
Valve disease	Merendino and Manhas[1]	10	13	0 77	1	2	0 50	10 0	15 4	0 65
C	This study	50	37	1 35	2	8	0 25	4 0	21 6	0 19
Valve replacement	Merendino and Manhas[11]	32	7	4 6	10	2	5 00	31.2	28 6	1 09
A	This study	19	27	0 7	7	11	0 64	36 8	40 7	0.90

fact seems to contradict the general impression that the opposite situation is true

Discussion

The data on the prevalence of gallstones presented herein agrees in general with other information published previously Our Group B data may be compared with the extensive autopsy results of Newman and Northup[19] for gallstone prevalence only their data for Caucasians and Negroes in the United States was considered for this purpose Such a comparison shows that the rise in gallstone prevalence with age for persons with rheumatic heart disease (Group B) is substantially the same as for the undesignated general population of Newman and Northup Our Group C data, however indicates a contrasting trend with a decreasing prevalence of gallstones with increasing age beginning in middle age This effect for patients with valvular heart disease was reported as well by Merendino and Manhas[11] and cannot be readily explained

Of much interest is the completely different trend that appears in prosthetic heart valve recipients (Group A) A striking increase in gallstone prevalence with age is apparent with a peak occurring in the 50 to 60 year decade In that decade our prosthetic valve recipients are subject to a prevalence of gallstones that exceeds Group B and Group C by a factor of five The reason for this trend is unknown but it may be influenced by the relatively small sample size and thus should be viewed with some reservation The difference in magnitude however, probably is due to increased red cell destruction and bilirubin production

A comparison of our results with the data of Merendino and Manhas[11] is pertinent Their Group B is comparable to our Group A patients with prosthetic heart valve replacement However the differences should be noted there are significant differences between our study and their study with respect to male/female ratio ethnic composition valve-site involvement and group size Their study groups were somewhat smaller than ours, and were almost entirely Caucasian But the major difference is that their prosthetic valve group consisted mostly of male aortic valve recipients whereas nearly 40 per cent of our Group A were female mitral valve recipients Despite these differences the trend of our data for prevalence of gallstones with age is in agreement with the data of Merendino and Manhas In absolute magnitude however our prevalence rates are somewhat higher than theirs

Additional insight may be gained from Table III which summarized the various data with respect to male/female ratio The last column on the right represents the ratio of percentage of males with gallstones (in a given group) to the percentage of females with gallstones The values for Groups B and C and corresponding data reflect the frequent observation that the prevalence of gallstones in males is substantially lower than among females In prosthetic valve recipients (Group A) however it appears that males are about as likely to develop gallstones as females (See also Table I)

The mechanisms of gallstone formation have been discussed in detail elsewhere [7, 20, 21] Gallstones associated with hemolytic disease have been observed in hereditary spherocytosis [2, 23] and sickle cell anemia [24] In the case of prosthetic heart valve recipients gallstones are thought to arise from bilirubin production resulting from hemolysis [7]

Mechanical trauma to red cells in valvular disease and prosthetic replacement frequently has been ascribed to turbulence[4, 7] or excessive fluid shear stresses[5] The hypothesis of turbulence generated hemolysis would appear to gain credence from the adverse effects of exercise observed in patients with valvular heart disease[2] or in recipients of valve prostheses[7, 9, 1, 26] However several investigators have expressed doubt that turbulence by itself is a primary cause of mechanical hemolysis[9, 10, 25] The hypothesis that hemolysis arises mainly from turbulence is probably too simplistic

It has been shown by Blackshear[2, 2] that extreme shear stresses associated with intense turbulence far greater than might be expected physiologically are required to produce significant hemolysis in blood flowing far distant from surfaces Turbulence could however influence red cell encounter with surfaces and affect other interfacial phenomena In the case of paravalvular leaks regurgitation may produce an increased frequency of red cell encounters with surfaces and turbulence may not be the major source of hemolysis Blackshear and other investigators believe that mechanical hemolysis is due primarily to the interactions of red cells with surfaces

Two of the 18 patients with gallstones (11 per cent) in Group A subsequently have developed symptoms of cholecystitis requiring cholecystectomy In neither instance however were the removed stones analyzed for bilirubin content We do not plan elective cholecystectomy in the other 16 patients at this time because the benefit to risk ratio does not appear to warrant this especially because all of the patients are receiving anticoagulant therapy

Conclusions

The results of this study have established that the prevalence of gallstones in patients with heart valve prostheses is significantly greater than in patients with mild or severe valvular heart disease without valve replacement Apparently the formation of gallstones may result from even mild mechanical hemolysis Valve prosthesis recipients should be evaluated carefully for symptoms of gallbladder disease at periodic intervals especially late after valve replacement To further define the problem we recommend that gallstones removed from prosthetic heart valve patients at surgery or at autopsy be analyzed for chemical composition especially to determine the existence of higher than average bilirubin content even in the case of calcium stones

Summary

The results of this investigation reveal that 39 per cent of patients in a study group of 46 patients with heart valve prostheses had gallstones if they survived 18 months or longer following valve replacement In contrast the prevalence of gallstones in a general population of autopsied rheumatic heart disease patients including those who had been operated for severe valvular heart disease and had not survived for more than one month was only 12 per cent These findings suggest that gallstones are a frequent late complication of heart valve replacement

The authors are indebted to Jean T Ikegami B S R N and Ellen Batista B S R N., for assistance in assembling sorting and compiling patient records

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The influence of atrial systole on ventricular capture by failing artificial pacemakers II Experimental observations

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The efficacy of ventricular capture by failing artificial pacemakers can be influenced by atrial activity Twenty six cases have been reviewed recently Two hypotheses have been advanced to explain this phenomenon One theory invokes an electrotonic interaction (Wedensky facilitation or inhibition) between the pacemaker stimulus and the atrial depolarization (The Wedensky effect is a separate phenomenon and is not considered in this report) The other theory postulates that atrial systole influences the efficacy of capture by altering the physical contact between the pacing electrode and the ventricular myocardium The present study was undertaken to reproduce this phenomenon in the dog and to ascertain which of these two mechanisms was operative The results strongly support the mechanical hypothesis

Methods

Mongrel dogs of either sex weighing 10 to 23 kilograms were anesthetized with sodium pento barbital (30 mg /Kg intravenously) and given additional doses as required Following a right thoracotomy the heart was suspended in a peri cardial cradle In some dogs the right upper lobe of the lung was excised to facilitate exposure A Harvard respirator provided ventilation

Atrioventricular block was created in one of two ways The ends of two pieces of fine (0 005 inch diameter) Teflon coated steel wire were bent to form hooks and were inserted through the right atrial wall into the region of the His bundle After recording a His bundle electrogram to verify the position a strong electric shock (20 to 150 joules) was passed through the heart using both wires as one pole and a large (8 7 cm diameter) metal paddle applied to the left ventricle as the other pole [2] Complete heart block was achieved in six dogs and first degree block (A V = 139 to 149 *msec) in one dog* Complete heart block was produced in an additional five dogs by injecting formalin into the His bundle [3]

The mid right atrium was paced through a close bipolar epicardial electrode The right ventricle was stimulated through a transvenous bipolar pacing catheter (USCI No 007152) the position of this catheter in the right ventricle was adjusted by trial and error until atrial systole exerted an influence on the test stimulus All stimuli were of 3 msec duration and were passed through isolation transformers The strength of all stimuli except the ventricular test stimulus (Vs) was two to three times threshold

Fig 1 illustrates the stimulation patterns employed in this study The atrium and ventricle were sequentially paced with a delay of 100 msec and with a train of 9 to 20 (usually 10) basic stimuli In Fig 1 the last of these are designated As_9, Vs_9, As_{10}, Vs_{10}. (Stimuli are denoted by the subscript "s" and the corresponding beats are designated without the subscript for example stimulus As_9 gives rise to beat A_9.) In any given experiment the cycle length of the basic stimuli

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Information for authors

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delivered at the end of expiration This was accomplished by matching the number and cycle length of the basic stimuli to the respiratory rate The timing was checked by means of an electrical signal elicited from the respirator at the onset of inspiration

In all experiments a standard lead electrocardiogram a close bipolar mid right atrial electrogram the ventricular stimuli and the respiratory signal were recorded The A Vs interval was measured from the intrinsic deflection of the atrial electrogram to the test stimulus The A A interval was measured from one intrinsic deflection to the other The capture by Vs was judged by examining the electrocardiogram for the presence or absence of a QRS immediately following Vs

Right atrial pressure was measured through a transvenous catheter or through a large bore (4 5 mm internal diameter) copper tube inserted in the right atrial appendage These were connected to a Statham transducer (model P23BC) interfaced with an Electronics for Medicine amplifier (model SGA) The transducer was calibrated against a mercury manometer All pressures were measured at the time Vs occurred and were measured to the nearest 0 5 or 1 0 mm Hg

All data were recorded on a TEAC tape recorder (model R 351 F) and were later photographed on continuously moving (25 mm /sec) film with a Grass Kymograph camera (model C4 K) The photographic image was enlarged and the data were measured with an accuracy of at least ± 5 msec Time calibrations were provided both by a digital interval generator (built by W J Mueller) and by a Tektronix interval generator (model 180A)

The statistical tests used were Chi squared derived from a contingency table with Yates correction where appropriate Student s t test for the difference of the means and the Wilcoxon two sample test for the unpaired case •

Results

Facilitation and inhibition of Vs Facilitation of ventricular capture by Vs is illustrated in Fig 2 In the control state (Fig 2*A*) Vs did not excite the ventricle when As was omitted and an atrial escape beat (AE) occurred after Vs In the test condition (Fig 2*B*) Vs captured the ventricle when a single atrial beat (A) preceded Vs by 88 msec Note that the right atrial pressure coincident with Vs was low in the absence of A (Fig

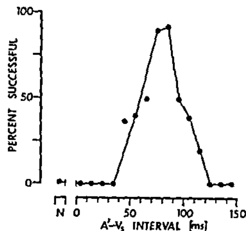


Fig 3 Facilitation of Vs *Abscissa* the A Vs interval in msec Data are plotted in 10 msec groups i.e 0 to 10 11 to 20 21 to 30 etc. *N'* refers to data collected when As was omitted, and an atrial escape beat (*AE*) occurred after Vs *Ordinate* the per cent of Vs that was successful in ventricular capture at any given A Vs interval. Total number of Vs = 666 Experiment performed on Apr 14 1977

2*A*) and high in the presence of A′ (Fig 2*B*) The time course of facilitation was examined by placing A at various times before Vs The results of one such experiment are shown in Fig 3 When the A Vs interval was less than 41 msec or greater than 110 msec Vs did not excite the heart However when the A Vs interval was 41 to 110 msec A facilitated ventricular capture by Vs Inhibition of ventricular capture was demonstrated in other experiments of the same design In six dogs either facilitation or inhibition of ventricular capture could be alternatively elicited by changing the position of the pacing catheter in the ventricle an example of this is presented in Fig 4 in which all of the data are from the same dog In this figure, A facilitated Vs when the A Vs interval was 51 to 140 msec and A inhibited Vs when the interval was 61 to 170 msec In most experiments A affected the efficacy of Vs when the A Vs interval was 41 150 msec the narrowest effective range observed was 31 to 110 msec and the widest effective range was 11 to 160 msec Faster basic driving rates tended to give narrower ranges of effective A Vs intervals but this observation was not systematically examined

Experiments in which the efficacy of Vs was influenced by a single atrial beat (A) were performed in 11 dogs facilitation was shown in seven and inhibition in eight Eleven complete curves similar to those shown in Figs 3 and 4 were constructed from these experiments

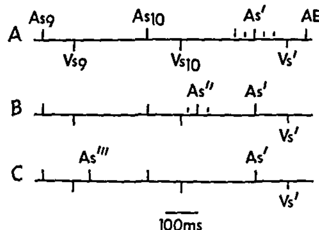


Fig 1 Stimulation patterns Vertical lines above and below the horizontal line represent stimuli delivered to the atrium and ventricle respectively The strength of the test stimulus (Vs) was less than that of the basic stimuli (Vs Vs_{10}) *The broken lines in panels A and B* indicate that As and As may assume various temporal positions Time calibration = 100 msec

was constant, the cycle lengths of all the experiments varied between 220 and 380 msec (mean = 323 msec) A ventricular test stimulus (Vs′) was then delivered at approximately the same interval as the basic stimuli, the test stimulus was never premature enough to encroach upon a possible zone of supernormal excitability The purpose of this test stimulus (Vs′) was to imitate a failing pacemaker, hence, the strength of Vs′ was adjusted to a value that was barely successful or barely unsuccessful in exciting the heart

The influence of atrial systole on the efficacy of Vs′ was studied by introducing one or more atrial stimuli (As , As ′, As‴) as illustrated in Fig 1 The influence of atrial systole on Vs′ was demonstrated as follows In the control situation no atrial stimulus was delivered before Vs′, and an atrial escape beat (AE) occurred after Vs′ (Fig 1*A*) In the test situation, a single atrial stimulus (As′) was delivered at a variable interval before Vs′ (Fig 1*A*) The phenomenon under study was present when a suitably timed atrial beat (A′) changed the excitatory efficacy of Vs′ as compared to control (no As)

The mechanism of this phenomenon was investigated by altering the hemodynamic performance of the atrial beat (A′) immediately preceding Vs′ The purpose of these experiments was to dissociate partially the hemodynamic and electrotonic effects of A′ Fig 1*B* shows a sequence that decreased the strength of the contraction of A′ as reflected by the right atrial pressure Holding As in a fixed temporal position another atrial stimulus (As′) was interpolated at various times after the last basic beat (Fig 1*B*) In other

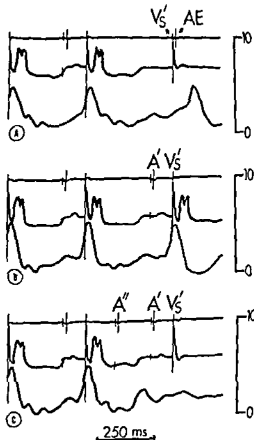


Fig 2 Facilitation of Vs and interpolation of A In each panel *top line* = atrial electrogram *middle line* = electrocar diogram *bottom line* = right atrial pressure *Panel A* control *Panel B* facilitation (A Vs = 88 msec) *Panel C* interpolation of A (A Vs = 88 msec A A′ = 15? msec.) The figures were traced from original photographs. The records of the ventricular stimuli were omitted Time calibra tion *(below)* = 250 msec Pressure calibrations *(right)* = 0 to 10 mm Hg Experiment performed on March 2 19?7

experiments, the contraction of A′ was enhanced by interpolating an atrial stimulus (As′) in the penultimate diastole (Fig 1C) The position of As As‴ was held constant, and the position of As was usually, but not always, fixed

That the excitatory efficacy of Vs was in fact being influenced by A′ was verified repeatedly After at most every tenth Vs , the atrial stimulation sequence was changed in such a way that the efficacy of Vs should change too For example if Vs′ excited the ventricle with A′ preceding Vs′ by 100 msec , then non capture by Vs′ in the absence of A′ was confirmed regularly Data were accepted for analysis only if such a reversal of effect occurred within four test cycles

Early in the study it became apparent that respiration had an independent effect on the efficacy of Vs This effect was characterized by failure of capture on inspiration and was probably caused by movement of the heart or catheter To compensate for this respiratory effect all Vs were

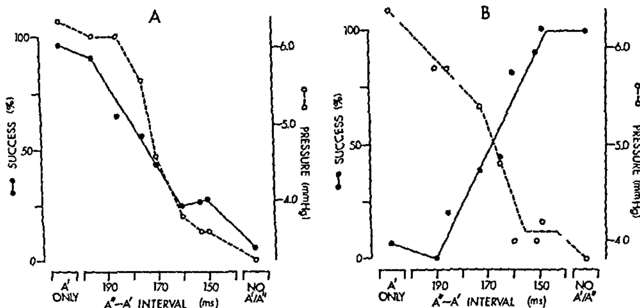


Fig 6 Facilitation (*panel A*) and inhibition (*panel B*) of Vs and interpolation of A (*both panels*) *Abscissa* NO A/A control *A ONLY* first test condition *A A INTERVAL* se ond test condition the time interval in msec. between these beats *Left ordinate* (●) the per cent of Vs that was su cessful in ventricular capture at any given stimulation pattern Right ordinate (o) the arithmetic average of all the right atrial pressures recorded during any given stimulation pattern In these experiments, the A Vs' interval was constant at 100 msec until the A A interval fell below 160 msec at which point the A Vs interval was 85 to 100 msec Total number of Vs = 687 (*panel A*) and 431 (*panel B*) Experiment performed on March ?8 1977

aberrant or if the A Vs interval shortened by more than 15 msec as compared to the initial test condition (A ONLY) In all dogs studied with an interpolated A a reduction of the pressure generated by A and a nullification of the effect of A on Vs were seen at A A intervals which produced no aberration of A and no change in the A Vs interval

Interpolation experiments with enhancement of the contraction of A In some experiments the control condition was that the efficacy of Vs' was not influenced by the presence the timing (A Vs interval) or the absence of A alone (Fig 7*A*) However when an atrial beat (A) was interpolated in the penultimate cycle the hemodynamic force of A was enhanced and A then exerted an effect on the efficacy of Vs (Fig 7*B*) In Fig 7*A* the atrial pressure at the time of Vs was the same as during the basic beats and Vs did not excite the ventricle In Fig 7*B* interpolation of A caused an increase in the pressure generated by A and A then facilitated Vs The change in the efficacy of Vs was not due solely to the presence of A This was demonstrated in three dogs by changing the A Vs interval while leaving A in a fixed position (not illustrated) Vs was influenced only during a specific range of A Vs intervals (40 to 150 msec)

The results of all the experiments of this type are summarized in Table I (Experiments with a variable A Vs interval are excluded) In all dogs interpolation of A significantly increased the pressure generated by A' and the hemodynamically enhanced A then significantly changed the efficacy of Vs

Atrial pressure and efficacy of Vs There was an excellent correlation between the level of the atrial pressure (coincident with Vs) and the efficacy of Vs (Fig 8) An increasing pressure was associated with greater facilitation or greater inhibition of Vs by A Moreover the correlation between pressure and success (Fig 8) was independent of the stimulation pattern employed An increase in pressure was accomplished by an atrial systole (A) alone with suitable timing (A Vs intervals of approximately 40 to 150 msec) by hemodynamically enhancing A with an interpolated beat (A) or by an A with a long A A interval A decrease in pressure was achieved by omitting As so that an escape beat occurred after Vs by relatively short or long A Vs intervals or by interpolating a beat (A) at a suitable interval

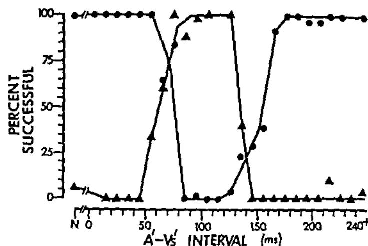


Fig 4 Alternate facilitation and inhibition of Vs in the same dog *Abscissa and ordinate* are identical to those in *Fig 3* (▲) Facilitation total number of Vs = 393 (●) Inhibition total number of Vs = 863 Experiment performed on Mar 29 1977

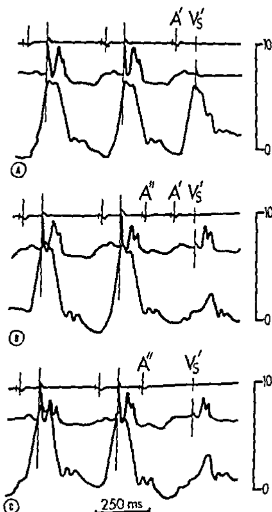


Fig 5 Inhibition of Vs and interpolation of A″ Data records and calibrations are the same as in *Fig 2* *Panel A* inhibition (A′ Vs = 95 msec) *Panel B* interpolation of A (A Vs = 95 msec A A′ = 132 msec) *Panel C* A alone (A Vs = 227 msec) Traced from the original photographs. Experiment performed on March 2 1977

Interpolation experiments with weakening of the contraction of A′ In Fig 2*B* A′ facilitated Vs′ When an atrial beat (A″) was interpolated immediately before A′, the facilitation was abolished, and Vs′ did not excite the ventricle (Fig 2*C*) Another experiment of this type, but with opposite conditions, is shown in Fig 5 In the control state (not illustrated), As′ and As″ were omitted, and Vs excited the ventricle In Fig 5*A*, A′ alone inhibited ventricular capture by Vs However, when both A′ and A″ were present (Fig 5*B*), the inhibition disappeared and Vs′ again excited the ventricle In both experiments interpolation of A′ did not change the appearance of A′ on the electrocardiogram or electrogram, but this interpolation did impair greatly the hemodynamic performance of A′ as revealed by the lower pressure at the time Vs occurred (compare Figs 2*B* and 2*C*, and Figs 5*A* and 5*B*) Fig 5*C* confirms that A′ was hemodynamically ineffective in Fig 5*B*

Gradations in the extent of hemodynamic impairment of A′ were produced by varying the A″ A′ interval while holding the position of A′ constant Fig 6 illustrates the results of two such experiments In Fig 6*A* in the control state (NO A′/A″) the atrial pressure was low, and Vs did not excite the ventricle In the first test condition (A′ ONLY), the pressure was high and Vs captured the ventricle When A″ was interpolated at progressively shorter A′ A′ intervals (A ′ A′ INTERVAL) the atrial pressure generated by A fell toward the control value and the facilitation of Vs′ by A was progressively eliminated Following a change in the position of the pacing catheter, the data in Fig 6*B* were obtained from the same dog that was represented in Fig 6*A* Interpolating A″ at decreasing A″ A′ intervals resulted in a progressive loss of the inhibition of Vs′ by A′ and a progressive fall in the atrial pressure toward the control value (Fig 6*B*) In both Figs 6*A* and 6*B* at short A″ A′ intervals the hemodynamic effect of A′ became negligible and the efficacy of Vs approached that seen in the absence of both A″ and A Moreover, the magnitude of the influence of A′ varied directly with the pressure generated by A′

Experiments of this type were done in five dogs, facilitation was reversed in four and inhibition in four Seven complete curves of the kind shown in Fig 6 were constructed from the data

At very short A As′ intervals (< 150 msec) either As failed to excite the atrium or the As′ A latency increased and A′ became grossly aberrant Data were rejected from analysis if A′ was

Table I Summary of the experiments in which interpolation of A ' enhanced the hemodynamic performance of A

Date of experiment	A absent		A present		Absent vs present
	Per cent Vs successful	Average RAP ± SD	Per cent Vs successful	Average RAP ± SD	p value
Facilitation					
4/15/77	00 (0/24)	4 3 ± 0 3	80 (41/51)	5 5 ± 0 3	< 0 001
5/3/77	11 (13/117)	4 5 + 0 5	92 (91/99)	6 2 ± 0 7	< 0 001
5/4/77	06 (2/35)	4 5 ± 0 3	94 (31/33)	4 8 ± 0 5	< 0 01 < 0 001
Inhibition					
4/15/77	98 (64/65)	5 5 ± 0 5	17 (18/109)	6 3 ± 0 7	< 0 001
5/3/77	79 (136/173)	5 8 ± 0 5	04 (6/136)	8 5 ± 0 7	< 0 001
5/5/77	89 (150/169)	–	06 (9/143)	–	< 0 001

First three horizontal rows = facilitation of Vs Last three horizontal rows = inhibition of Vs
Symbols and abbreviations A absent = control, A present and A absent A present = test condition, both A and A present The A Vs interval was constant in each experiment. *Per cent Vs successful* = the per cent of Vs' that was successful in ventricular capture under the conditions specified Numbers in parentheses are the actual number of Vs successful and the number tested *Average RAP* = the arithmetic average of all the right atrial pressures (RAP) recorded under the conditions specified *SD* = standard deviation. *Absent vs present* = statistical comparison of the efficacy of Vs' and the pressure data in the two conditions. *p value* = the result of testing efficacy with the Chi squared test, and of testing the pressure data with the Chi squared test the Student's t test and the Wilcoxon z value For each experiment every statistical test gave p < 0 001 except for the experiment of May 4 1977 in which the Chi square test and Student's t test for pressure data gave p < 0 01

that atrial systole caused motion of the pacing catheter in eight patients

Interpolation experiments In order to study these two hypotheses the present experiments were designed to dissociate partially the mechanical and electrotonic effects of the atrial beat (A) immediately before the test stimulus (Vs) Interpolation of an atrial beat (A) immediately before A resulted in a decrease in the hemodynamic performance of A and conversely interpolation of a beat (A) in the penultimate cycle resulted in an increase in the pressure generated by A Two observations support the idea that dissociation was achieved First the configuration of A on the electrocardiogram and atrial electrogram was unchanged after interpolation despite a significant change in the pressure generated by A Second interpolation of A or A undoubtedly caused some shortening of the action potentials of A as a result of the abrupt increase in atrial rate However the mechanical effects changed in opposite directions (increase or decrease in pressure) in the two types of interpolation experiments while the electrical effects changed in the same direction (shortening of the action potentials)

These experiments showed that an atrial depolarization by itself was insufficient to alter the efficacy of capture by the ventricular test stimulus (Vs) This was especially apparent in the mechanical enhancement experiments in which the normal atrial beat (A , control condition) did *not* affect the efficacy of the test stimulus (Vs)

Atrial pressure The enhancement or depression of hemodynamic performance seen in the interpolation experiments is a manifestation of the phenomenon of restitution[8] and may be studied in terms of changes in pressure However it almost certainly was *not the atrial* pressure itself that affected the efficacy of the test stimulus Proof that the changes in efficacy were caused by motion of the pacing catheter and/or ventricular myocardium and proof that this motion was caused by atrial systole could have been obtained by measuring the movements of these structures Technical limitations prevented such measurements *Nevertheless* the pressure measurements did verify the changes in hemodynamic performance did correlate well with the changes in efficacy of the test stimulus (Fig 8 and Table I) and did show that the atrial influence was mediated by a mechanical mechanism

Epicardial pacing In an earlier study using right ventricular epicardial electrodes Arbel and colleagues[9] observed that a suitably timed atrial beat increased the efficacy of capture by a low voltage stimulus This preliminary report was based on a single experiment conducted in a dog without atrioventricular block It might be argued that this observation is incompatible with the mechanical hypothesis since the stimulus was

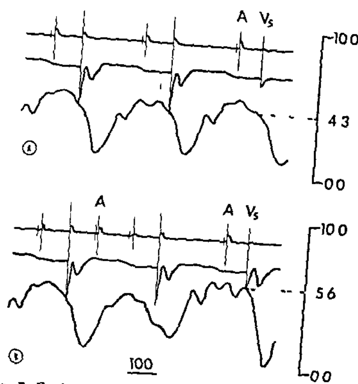


Fig 7 Facilitation of Vs when the contraction of A was enhanced by interpolation of A Data records are the same as in *Fig 2 Panel A* control *Panel B* interpolation of A A Vs = 75 msec in both panels The right atrial pressures coincident with Vs *are indicated by the numbers at the ends of the broken lines* Traced from the original photographs Time calibration (*below*) = 100 msec Pressure calibrations (*right*) = 0 0 to 10 0 mm Hg Experiment performed on April 15 1977

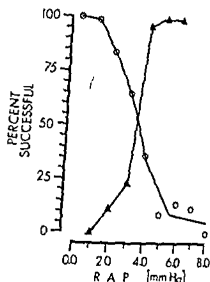


Fig 8 Atrial pressure and efficacy of Vs *Abscissa* right atrial pressure *(RAP)* in mm Hg *Ordinate* the per cent of Vs (occurring at any given level of pressure) that was successful in ventricular capture (▲) Facilitation total number of Vs = 303 (o) Inhibition total number of Vs = 566 Experiment performed on March 2 1977

immediately before A′ For example the data in Fig 8 came from experiments in one dog in which A′ alone was present at varying A Vs′ intervals, in which A was present with varying A″-A′ intervals, and in which As′ was omitted In total, 10 correlations of the type shown in Fig 8 were obtained in the six dogs in which technically adequate pressures were recorded

The strength of Vs′ When the strength of Vs′ was increased or decreased beyond the value that was barely successful or unsuccessful in ventricular capture A ceased to exert any influence on Vs regardless of the stimulation pattern used With reductions in strength all Vs failed with increases all succeeded

Discussion

These experiments have shown that a suitably timed atrial systole can frequently and consistently alter the efficacy of ventricular capture by a low voltage stimulus delivered to the right ventricular endocardium through a bipolar pacing catheter The results support the idea that this phenomenon is mediated by the mechanical effects of the atrial beat Without changing the appearance or timing of the atrial depolarization weakening of the contraction abolishes a preexisting atrial influence, and enhancement of the contraction establishes an influence where none existed before

Electrotonic hypothesis Most earlier reports favored an electrotonic mechanism as the explanation for the influence of atrial activity on the efficacy of pacemaker capture This hypothesis has been reviewed and analyzed recently [1] It is very unlikely that an electrotonic mechanism was operative in the experiments described here because of the distance separating the atria and the pacing electrode Because the space constant of the myocardium is very short,[5] an electrotonic current originating in the atria would be virtually extinguished before it reached the electrode in the right ventricle

Mechanical hypothesis Several authors have acknowledged the possibility of a mechanical explanation, but few have favored it [1] This hypothesis proposes that atrial systole alters the efficacy of capture by increasing or decreasing the contact between the electrode tip and the ventricular myocardium An atrial contraction could move the intra atrial portion of the catheter if the catheter were in close proximity to the atrial wall Alternatively, by augmenting left ventricular diastolic volume atrial systole could move the ventricular wall relative to the catheter This hypothesis has received some support from the report of Preston [6] who radiographically observed

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Epicardial pacing In an earlier study using right ventricular epicardial electrodes Arbel and colleagues observed that a suitably *timed* atrial beat increased the efficacy of capture by a low voltage stimulus This preliminary report was based on a single experiment conducted in a dog without atrioventricular *block It* might be argued that this observation is incompatible with the mechanical hypothesis since the stimulus was

delivered through epicardial electrodes However, the mechanical hypothesis does not require gross changes in the electrode contact, depending on the type of epicardial electrode used small changes in contact could result from atrial systole

In the present study, using a close bipolar electrode firmly hooked into the right ventricular epicardium, we were unable to show that atrial systole had any effect on the efficacy of the test stimulus (Vs′) These experiments were done in three dogs with and without atrioventricular heart block In those dogs with heart block, the stimulation pattern employed was the one illustrated in Fig 1*A*, in the dogs without heart block, the pattern employed was the one used by Arbel and associates [9] In contrast, in every dog adequately studied with a bipolar endocardial pacing catheter it was possible to show either inhibition or facilitation of the test stimulus by atrial systole

These results are consistent with the human case reports In 19 of the 20 cases in which sufficient information is available the pacing catheter was of the transvenous endocardial type [1] In the single case with an epicardial electrode, the catheter tip had migrated and was not securely fixed to the heart Thus both the experimental and clinical observations provide additional indirect support for the mechanical hypothesis

Clinical implications These experimental results combined with the radiographic observations of Preston[6] and the analysis indicating the applicability of the mechanical mechanism to the human cases [1] strongly suggest that the Wedensky phenomena (facilitation and inhibition) do not explain this particular type of pacemaker arrhythmia The examples of this arrhythmia[1] represent the primary and perhaps only situations in which these electrotonic mechanisms have been thought to occur in man Although there is no a priori reason why the Wedensky phenomena cannot apply to human cardiac electrophysiology further investigations are needed to document their involvement Finally these experiments demonstrate the importance of mechanical events in the pathogenesis of a particular rhythm disturbance Consideration of the possibility of mechanical factors in arrhythmogenesis may well provide additional examples in the future

Summary

The mechanism by which atrial systole influences the efficacy of ventricular capture by a failing pacemaker was investigated in 12 dogs with atrioventricular heart block Atrial systole caused facilitation of ventricular capture in eight dogs, and inhibition of capture in 10 dogs Interpolating atrial extrasystoles caused an enhancement or depression of the hemodynamic performance of the atrial systole that affected the efficacy of the pacemaker stimulus These interpolation experiments showed that atrial systole influenced the efficacy of capture by a mechanical mechanism and not by an electrotonic mechanism Atrial systole probably caused motion of the endocardial pacing catheter and/or ventricular myocardium This motion increased or decreased the contact between the pacing electrode and the endocardium with subsequent changes in the efficacy of capture In three dogs with pacing through epicardial electrodes, atrial systole had no effect on the efficacy of capture

We would like to thank Dr Eugene Lepeschkin who initially suggested some of these ideas

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Case reports

Systemic hypertension after surgical treatment of a congenital arteriovenous malformation

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Systemic hypertension though uncommon in childhood is usually associated with a specific etiology such as renal disease coarctation of the aorta or pheochromocytoma We recently encountered severe systemic hypertension resulting from surgical obliteration of a congenital arteriovenous malformation a heretofore unreported observation in childhood The purpose of this report is to document this unusual cause for hypertension suggest a mechanism for its genesis and recommend appropriate therapy

Case report

K. S an 8-year-old Caucasian girl was noted at birth to have an arteriovenous fistula of the left thigh Because of hemorrhage following minor trauma multiple vessels supplying the malformation were ligated at ages 4 and 5 During the subsequent two years a lump developed as the leg size increased At age seven she was admitted to The Children s Hospital Medical Center in Boston On admission (Oct 2 19 3) a large arteriovenous malformation of the left thigh was present other findings are outlined in Table I A left femoral arteriogram (Fig 1A) demonstrated an extensive arteriovenous malformation of the left leg extending from the inguinal ligament to just below the knee She was treated with 1 000 rads of radiation (divided over three days) and a one month course of prednisone (1 5 mg /Kg /day) She was readmitted to the hospital on Nov 14 1973 (Table I) On Nov 15 1973 the left hypogastric and profunda femoris arteries and all

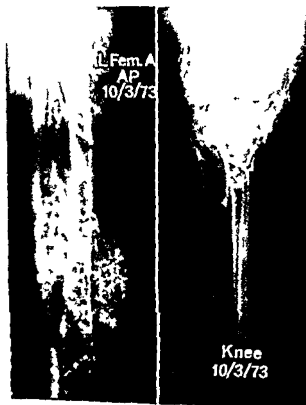


Fig 1 A through C Arteriograms before *(A)* two weeks after *(B)* and ei ht months after *(C)* surgical obliteration of a congenital arteriovenous malformation L Fem A = left femoral artery L Sup Fem = left superficial femoral artery L Il A = left iliac artery AP = anterior posterior projection

feeding branches of the left superficial femoral artery were ligated. Her immediate postoperative course was accompanied by hypertension (1 0/110 mm Hg) (Fig 2) a decrease in central venous pressure (20 cm of water to 7 cm of water) and a grand mal seizure On Nov 19 1973 a left femoral

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Table I Clinical and laboratory findings

Date	10/2/73	11/14/73	11/26/73	7/11/74	10/31/74	[illegible]
Heart rate (beats/min)	156	136	80	100	100	110
Blood pressure (mm Hg)	114/70	125/75	138/95	110/60	110/60	129/64
Murmurs						
Systolic	Grade 2/6	same	same	same	same	same
Diastolic	Grade 2/4	same	none	none	none	none
Loud S_3	yes	yes	none	none	yes	yes
Hepatomegaly	yes	yes	none	none	none	none
Chest x ray (C T ratio)	62	63	56	54	56	60
Electrocardiogram	BVH	BVH	–	normal	normal	normal
Branham reflex	*Rest* *Compression*				*Rest* *Compression*	
Heart rate	156 100	–	–	–	110 72	–
Blood pressure	114/70 130/95	–	–	–	110/60 124/98	–
Echocardiogram						
Heart rate	156 100	–	80	100	110 75	–
Stroke volume (ml /beat)	57 41	–	47	69	76 58	–
Cardiac index (L /Min /M)	10 4 5 2	–	4 7	8 6	10 3 5 5	–
Ejection fraction	62 63	–	74	62	58 60	–

Abbreviations BVH = biventricular hypertrophy C T Ratio = cardiothoracic ratio

arteriogram demonstrated decreased flow to the arteriovenous malformation above the knee but no significant change distally On Nov 27 1973 branches of the left popliteal and posterior tibial arteries were ligated Postoperatively she again developed hypertension (158/115 mm Hg) and a second seizure A technetium brain scan cerebral angiogram and multiple blood chemistry studies renal function studies 17 ketosteroids and renal arteriogram were all normal She was initially treated with hydralazine (5 to 7 mg) methyldopa (500 mg /day) and chlorothiazide (600 mg /day) without an effect on the blood pressure Finally when markedly elevated plasma renin activity was observed (peripheral venous blood 6 930 ng per cent/3 hours peripheral venous blood 8 171 ng per cent/3 hours left renal vein 10 320 ng per cent/3 hour right renal vein 11 660 ng per cent/3 hour) (Fig 2 Symbols *A B C* respectively) she was begun on propranolol (initially 10 mg /day then increased to 20 mg /day) with an immediate and marked reduction in both blood pressure and plasma renin activity (1 523 ng per cent/3 hours and 1 027 ng per cent/3 hours Fig 2 Symbols *D* and *E* respectively)

The PRA was assayed in blood taken from an antecubital vein in the recumbent position while on a diet containing between 70 to 90 mg sodium daily Plasma renin activity assay was by the method of Boucher and associates Normal values in our laboratory (while on a diet containing 70 to 110 mg sodium daily and obtained in the recumbent position) are up to 1 500 ng per cent/3 hours

Following her second surgery a femoral angiogram (Figure 1B) demonstrated a significant reduction in flow through the arteriovenous malformation An echocardiogram on Nov 26 1973 demonstrated a marked decrease in cardiac output (Table I) She was discharged from the hospital on propranol ol phenobarbital and dilantin Over the next six months she remained normotensive and the propranolol was discontinued On July 9 1974 an arteriogram demon trated that the arteriovenous malformation had reconstituted itself (Fig 1C) Four months after discontinuation of propranolol (Oct 31 1974) her blood pressure was 110/60 mm Hg however physical examination and echocardiogram suggested the reap pearance of high cardiac output (Table I)

She remained well until January 1975 when she developed ulcerations of the skin over the arteriovenous malformation on the anterior aspect of the left thigh She was hospitalized on Feb 8 1975 after bleeding from the ulcerations at that time her plasma renin activity was 920 ng per cent/3 hours (Fig 2 Symbol *F*) An arteriogram demonstrated further increase in size of the arteriovenous malformation Because of a massive sudden hemorrhage her left leg was amputated on Feb 9 1975 Following the amputation she again developed significant systemic hypertension (155/106 mm Hg) Treat ment with intermittent doses of intravenous propranolol (0 3 mg) resulted in a rapid return of blood pressure to normal values

Discussion

Acute hypertension following temporary occlu sion of a large arteriovenous malformation is a well known phenomena (Branham s reflex) The occlusion of the fistula results in an acute increase in peripheral vascular resistance and thereby, blood pressure (Fig 3) However persis tent hypertension (seen in our patient) following surgical obliteration of a large arteriovenous malformation although previously reported[1] is



Fig 1B For legend see *Fig 1A*

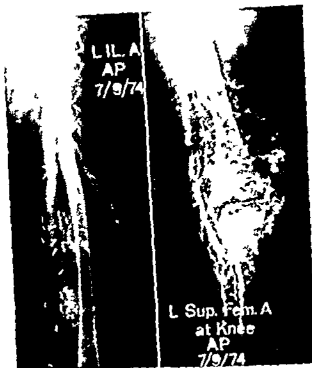


Fig 1C For legend see *Fig 1A*

poorly understood Holman has proposed that the transient elevation of systolic and diastolic pressure following closure of traumatic arteriovenous fistula is due to distention of the arterial bed by the volume of blood increased in the presence of the fistula The changes in blood volume following ligation of the fistula observed in patients and experimental animal studies form the basis for this thesis However in our patient this is not the only explanation since the development of hypertension was also associated with a markedly elevated PRA

The temporal association of increased plasma renin activity with the observed hypertension and the decrease in both plasma renin activity and blood pressure following the administration of propranolol a possible inhibitor of renin secretion (Fig 2) imply that the increased plasma renin activity may have contributed to the development of systemic hypertension seen in our patient The other medications hydralazine and chlorothiazide (all known to affect plasma renin activity[4] make it difficult to be certain that surgical ligation of the arteriovenous malformation was the only mechanism responsible for the elevation in plasma renin activity However inspection of Fig 2 shows no clear relationship between any of these drugs and PRA

The exact mechanism for the rise in plasma renin activity following ligation of an arteriovenous malformation is unknown The major hemodynamic effects observed were a decrease in central venous pressure (20 to 7 cm of water) a reduction in heart size (cardiothoracic ratio of 63 to 56) a reduction in cardiac output clinically and as determined by echocardiography (cardiac index decreased from 10 4 L /min /M preoperatively to 4 7 L /min /M postoperatively) and a decrease in stroke volume (57 ml /beat preoperatively to 47 ml /beat postoperatively) One might

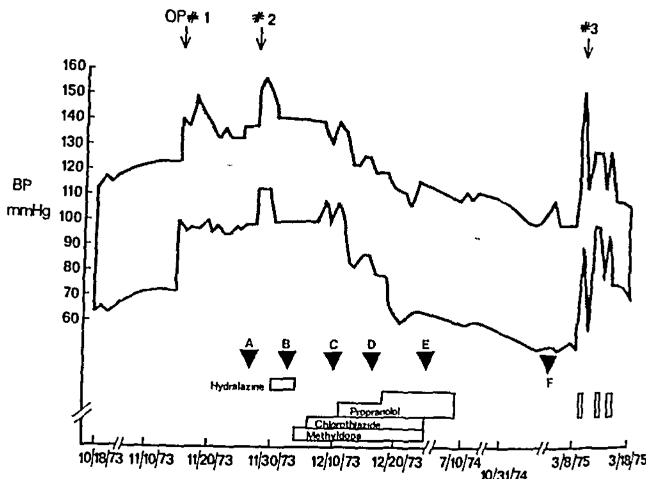


Fig 2 The temporal relationship between surgery blood pressure renin level and therapy in the management of a congenital arteriovenous fistula ▼ = plasma renin activity (ng %/3 hr) A = peripheral venous 6 930 B = peripheral venous 8 171 C = left renal vein 10 320 and right renal vein 11 660 D = peripheral venous 1 523 E = peripheral venous 1 027 F = peripheral venous 920 (Maximal normal value for mixed venous plasma renin activity 1500 ng %/3 hr)

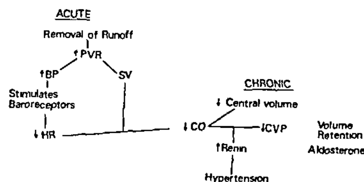


Fig 3 Etiology of hypertension after acute (cuff occlusion) and chronic (ligation) occlusion of a large systemic arteriovenous malformation In addition to the changes observed after acute removal of the runoff resection results in hypovolemia increased renin release and sustained hypertension Abbreviations *PVR* = peripheral vascular resistance *SV* = stroke volume *BP* = blood pressure *HR* = heart rate *CVP* = central venous pressure *CO* = cardiac output

speculate that these hemodynamic changes may be responsible for the observed rise in plasma renin activity

Blood volume is known to be a regulator of plasma renin activity A number of observations have linked high renin levels with hypovolemia and volume contracted states[5, 6] Atrial pressures and volume have also been demonstrated to influence renin secretion in the dog[7, 8] Since Holman[3] has demonstrated a decrease in plasma volume in five patients following closure of an AVM, and since our patient experienced a decrease in central venous pressure cardiothoracic ratio cardiac output and stroke volume it seems likely that the central blood volume also decreased in our patient after closure of the arteriovenous malformation It is therefore possible that having been in a chronic high volume high output state that the acute decrease in central blood volume after ligation of the arteriovenous malformation was perceived as being abnormal and thereby causing a rise in plasma renin activity Therefore the rise in plasma renin activity following ligation of the arteriovenous malformation probably represents an attempt to maintain volume homeostasis and the resulting hypertension is a byproduct of these compensatory response (Fig 3)

Regardless of the mechanism, ligation of the

congenital arteriovenous malformation resulted in an increased PRA and in systemic hypertension The case clearly demonstrates the importance of understanding the genesis of the hypertension so that proper treatment may be administered Initially the patient was ineffectively treated with hydralazine and chlorothiazide both known to cause some increase in renin secretion [10] Only after finding that an abnormality in the renin-angiotensin system was responsible for the hypertension was the hypertension effectively controlled with propranolol an inhibitor of renin secretion

Summary

The development of systemic hypertension in an eight year old girl after resection of a large arteriovenous malformation is described The hypertension was related to an elevated plasma renin activity and was controlled with propranolol A possible mechanism for the rise in plasma renin activity is postulated

We wish to thank Dr Clifford Barger for his suggestions and advice in preparing this manuscript

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The influence of atrial activity on ventricular capture by failing artificial pacemakers I

Report of two new cases and review of the literature*

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Several reports[1-9] have documented cases where the success or failure of ventricular capture by a stimulus from a failing pacemaker depended on the time interval between the stimulus and a preceding P wave Stimuli falling within a critical P S interval (the time interval between the beginning of the P wave and the stimulus artifact) exhibited enhanced or diminished efficacy of capture compared to stimuli falling outside this critical interval This report makes a detailed study of this phenomenon in two new cases and discusses its possible mechanisms

Methods

The P S intervals corresponding to the effective and ineffective stimuli in Cases 1 and 2 were measured with an accuracy of ±10 msec from electrocardiograms recorded at 50 mm/sec The P S intervals obtained from published electrocardiograms were measured with an accuracy of ±20 msec In some published records it was not possible to identify P waves and consequently not all of the published material was analyzed Pacemaker stimuli falling within the T wave of a previous ventricular beat were omitted from analysis since the ventricle then would have been in its refractory period and the stimulus ineffective regardless of its relation to the P wave

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Case reports

Case 1 In 1965 a 75 year old man was admitted to the Veterans Administration Hospital Ann Arbor Michigan with angina pectoris exertional dyspnea orthopnea and hypertension Examination showed a blood pressure of 170/88 mm Hg a II/VI systolic murmur at the apex a I/VI diastolic murmur at the left sternal margin and a diastolic extra sound The electrocardiogram revealed complete atrioventricular block and a spontaneous ventricular rhythm at a rate of 40 beats/minute On roentgenogram the heart size was normal and the mitral annulus was moderately calcified An asynchronous pacemaker generator (Medtronic Model No 5870 C code VOO*) was implanted with a transvenous bipolar pacing catheter (Medtronic Model No 5816) the tip of which was in the right ventricle This functioned normally and the man was discharged

Seven months later the patient was readmitted with a complaint of dizziness when he took a deep breath The electrocardiograms revealed that the pacemaker stimulus failed to excite the heart during deep inspiration A chest roentgenogram showed that the tip of the pacing catheter had moved farther away from the apex of the ventricle The catheter was repositioned with improvement in function but roentgenograms continued to show suboptimal placement of the catheter tip in the right ventricle One week later the patient again had intermittent pacemaker failure at this time the success or failure of the stimulus bore no relation to respiration or to atrial systole A short course of prednisolone was given for presumed exit block around the tip of the pacing catheter (see Discussion section) The patient improved and was discharged One month later intermittent failure of the pacemaker was again documented Two months later the patient complained of a slow pulse but pacemaker failure was not documented

One year later (22 months after initial implantation) electrocardiograms recorded over a period of 42 days revealed intermittent failure of the pacemaker stimulus to excite the heart These electrocardiograms form the basis of this report

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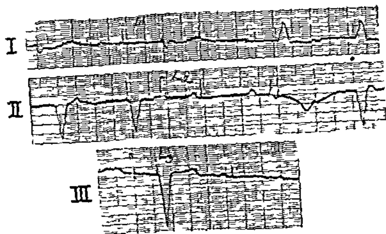


Fig 1 Case 1 Electrocardiographic Leads I (recorded Feb 12 1967) II and III (recorded Mar 24 1967) The dots above the strips indicate the positions of the pacemaker artifacts. Recorded at 50 mm /sec., one large horizontal division = 200 msec., two large vertical divisions = 1 mV

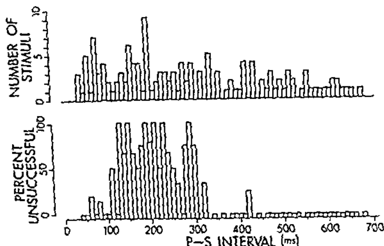


Fig 2 Case 1 *Top* Number of stimuli that occurred at each P S interval (time interval in msec between the stimulus artifact and the onset of the preceding P wave) Bottom Per cent of pacemaker stimuli that were unsuccessful in ventricular capture at each P S interval.

and are presented below Chest roentgenograms were unchanged Prednisolone and ephedrine were given for presumed exit block but were not effective (see Discussion section) Subsequently the old pacemaker system was removed new pacemaker leads were sutured to the left ventricular epicardium and a new generator was implanted Testing of the explanted generator by the manufacturer showed a 100 per cent depletion of cell No 1 with a total generator output of 4 1 volts compared to 5 0 volts originally The new pacemaker system functioned normally for the next 5 years, at which time the patient died of uremia At autopsy the heart weighed 450 grams, there was moderate atherosclerosis of the coronary arteries and the mitral valve was calcified and stenotic

Case 2 In 19 3 a 73-year-old woman was admitted to University Hospital, Ann Arbor Michigan with angina pectoris and nocturnal and exertional dyspnea Examination revealed a blood pressure of 195/84 mm Hg moderately severe kyphoscoliosis and pectus excavatum a previous left mastectomy a II/VI systolic murmur at the left sternal margin and third and fourth heart sounds The electrocardiogram was normal except for 2 1 atrioventricular block. A moderately enlarged heart and the thoracic deformities noted above were present on the roentgenogram A unipolar demand generator (Medtronic Model No 5943 code VVI) and transvenous pacing catheter (Medtronic Model No 6909) the tip of which was in the right ventricle were installed Initially the pacemaker functioned normally but nine days after implantation the pacemaker stimulus intermittently failed to excite the heart The electrocardiograms documenting this failure registered for four days form the basis of this report and are presented below A repeat roentgenogram of the chest, when compared with one taken a week earlier showed a new upward displacement of the tip of the pacing

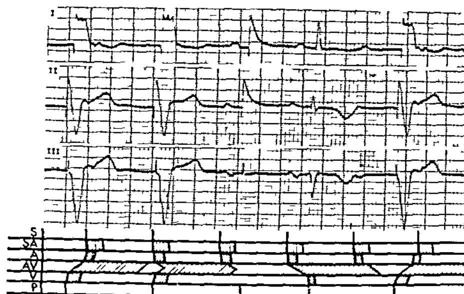


Fig 3 Case 2 Non simultaneous electrocardiographic Leads I II and III The diagram at the bottom is a proposed analysis of Lead III Recorded at 50 mm /sec one large horizontal division = 200 msec two large vertical divisions = 1 mV Abbreviations *A* = atrium *AV* = atrioventricular junction *P* = pacemaker *S* = sinus node *SA* = sinoatrial junction *V* = ventricle *The stippled areas* (in A and V) indicate the P waves and the QRS complexes *The striped areas* (in SA and AV) indicate the refractory periods of those tissues

catheter The tip continued to be located near the apex of the right ventricle The catheter was repositioned with subsequently normal pacing function for the next three years (up to the time last seen)

Results and review

The electrocardiographic data for Case 1 are presented in Figs 1 and 2 In Fig 1 the P waves appear at a faster rate than the pacemaker stimuli In Lead I the first two beats are ventricular escape beats and the last two beats are paced The first and third pacemaker discharges (artifacts) do not capture the ventricle because they fall in the refractory periods of the escape beats The second pacemaker discharge appears outside of the refractory period but does not capture the ventricle it is preceded by a P wave with a P S interval of 275 msec In Lead II, the first second and fourth beats are paced the third beat is an escape beat A P wave precedes the third pacemaker discharge by 155 msec and this discharge does not excite the ventricle The fourth artifact falls in the refractory period of the escape beat In Lead III the single beat present is paced, the second pacemaker stimulus does not excite the ventricle (P S interval = 140 msec) In this figure note the variation in P S intervals associated with inhibition of ventricular capture by atrial activity note that the electrocardiogram shows only Ta waves but no ventricular activity after the stimuli preceded by P waves (second stimuli in Leads I and III third stimulus in Lead II), and note that there are no conducted beats present

Fig 2 summarizes all of the electrocardiographic data, 139 stimuli are analyzed For P S intervals between 110 and 320 msec 68 per cent of the stimuli were unsuccessful in excitation For P S intervals less than 110 msec or greater than 320 msec 4 per cent of the stimuli were unsuccessful This difference is statistically significant (Chi squared with Yates correction = 60 9 $p < 0\,001$)

Case 2 is illustrated in Figs 3 to 5 In Fig 3 the first complex in each lead consists of a unipolar pacemaker artifact followed by and superimposed upon a wide QRS which in turn is followed by a biphasic P wave As indicated in the analysis of Lead III at the bottom of the figure the first complex is a paced beat with retrograde atrial activation The second complex is similar to the first except that it shows no separate P wave instead a non conducted sinus P wave is superimposed on the paced QRS complex The third complex consists of a sinus P wave followed 170 to 200 msec later by a pure pacemaker artifact This artifact has an initial slender upward deflection followed by a broad terminal portion corresponding to the decay of the electrode polarization [11] Since the generator was located in the right infraclavicular fossa the vector of the pacemaker artifact is nearly perpendicular to Lead III where the size of the artifact is minimal Since both the

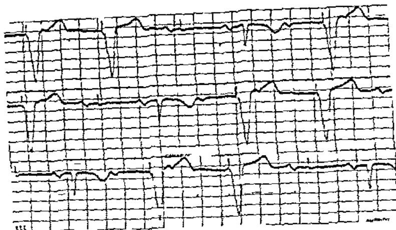


Fig 4 Case 9 Continuous electrocardiographic Lead III Recorded at 50 mm/sec one large horizontal division = 200 msec two large vertical divisions = 1 mV

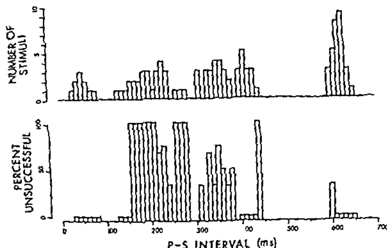


Fig 5 Case 9 *Top* Number of stimuli occurring at each P S interval (defined as in *Fig 2*) *Bottom* Per cent of pacemaker stimuli that were unsuccessful in ventricular capture for each P S interval

paced beats (first second and fifth complexes) and the conducted beats (fourth complexes) show a large negative QRS in Lead III a fusion beat also would have had a large negative QRS in Lead III However the negative deflection following the third stimulus is too small to have been part of a fusion beat Hence it is apparent that this stimulus was inhibited by the preceding atrial activity and that there was no ventricular activation following the third stimulus The fourth complex is a conducted beat with a P R interval of 195 msec Atrioventricular conduction occurred at this point because as indicated in the diagram the preceding pacemaker stimulus was ineffective because the preceding P wave was blocked and because the underlying rhythm before pacing was 2 1 atrioventricular block The conducted beat inhibited the pacemaker generator as indicated by the broken line in the diagram The last complex is similar to the first one

Fig 4 shows a longer example of the repeating pattern intermittently present in this patient Two paced beats are followed by an unsuccessful stimulus and then by a conducted beat This pattern results from the relative atrial and ventricular rates the demand nature of the pacemaker the 2 1 atrioventricular block and the influence of atrial activity on the pacemaker

Fig 5 presents the analysis of 105 stimuli For P S intervals between 160 and 380 msec 69 per cent of the stimuli were unsuccessful in excitation For P S intervals outside this range 4 per cent of the stimuli were unsuccessful This differ

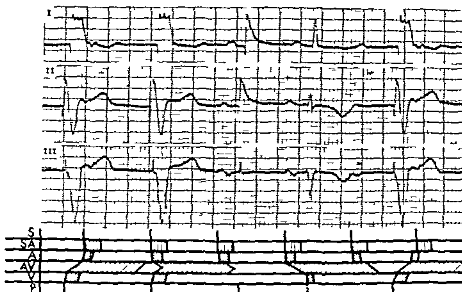


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The electrocardiographic data for Case 1 are presented in Figs 1 and 2 In Fig 1 the P waves appear at a faster rate than the pacemaker stimuli In Lead I the first two beats are ventricular escape beats and the last two beats are paced The first and third pacemaker discharges (artifacts) do not capture the ventricle because they fall in the refractory periods of the escape beats The second pacemaker discharge appears outside of the refractory period but does not capture the ventricle it is preceded by a P wave with a P S interval of 275 msec In Lead II the first second, and fourth beats are paced the third beat is an escape beat A P wave precedes the third pacemaker discharge by 155 msec and this discharge does not excite the ventricle The fourth artifact falls in the refractory period of the escape beat In Lead III the single beat present is paced, the second pacemaker stimulus does not excite the ventricle (P S interval = 140 msec) In this figure note the variation in P S intervals associated with inhibition of ventricular capture by atrial activity note that the electrocardiogram shows only Ta waves but no ventricular activity after the stimuli preceded by P waves (second stimuli in Leads I and III, third stimulus in Lead II), and note that there are no conducted beats present

Fig 2 summarizes all of the electrocardiographic data 139 stimuli are analyzed For P S intervals between 110 and 320 msec 68 per cent of the stimuli were unsuccessful in excitation For P S intervals less than 110 msec or greater than 320 msec 4 per cent of the stimuli were unsuccessful This difference is statistically significant (Chi squared with Yates correction = 60 9 $p < 0\ 001$)

Case 2 is illustrated in Figs 3 to 5 In Fig 3 the first complex in each lead consists of a unipolar pacemaker artifact followed by and superimposed upon a wide QRS which in turn is followed by a biphasic P wave As indicated in the analysis of Lead III at the bottom of the figure the first complex is a paced beat with retrograde atrial activation The second complex is similar to the first except that it shows no separate P wave instead a non conducted sinus P wave is superimposed on the paced QRS complex The third complex consists of a sinus P wave followed 170 to 200 msec later by a pure pacemaker artifact This artifact has an initial slender upward deflection followed by a broad terminal portion corresponding to the decay of the electrode polarization [11] Since the generator was located in the right infraclavicular fossa the vector of the pacemaker artifact is nearly perpendicular to Lead III where the size of the artifact is minimal Since both the

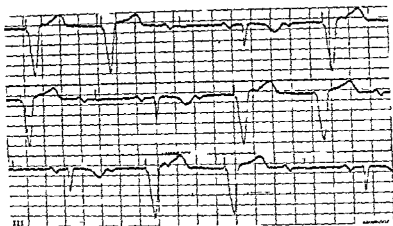


Fig 4 Case 2 Continuous electrocardiographic Lead III Recorded at 50 mm/sec one large horizontal division = 00 msec two large vertical divisions = 1 mV

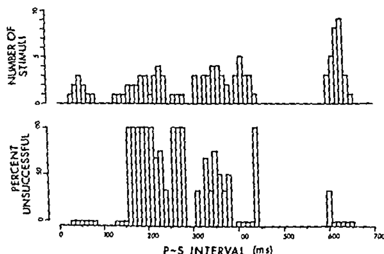


Fig 5 Case 2 *Top* Number of stimuli occurring at each P S interval (defined as in *Fig 2*) *Bottom* Per cent of pacemaker stimuli that were unsuccessful in ventricular capture for each P S interval

paced beats (first second and fifth complexes) and the conducted beats (fourth complexes) show a large negative QRS in Lead III a fusion beat also would have had a large negative QRS in Lead III However the negative deflection following the third stimulus is too small to have been part of a fusion beat Hence it is apparent that this stimulus was inhibited by the preceding atrial activity and that there was no ventricular activation following the third stimulus The fourth complex is a conducted beat with a P R interval of 195 msec Atrioventricular conduction occurred at this point because as indicated in the diagram the preceding pacemaker stimulus was ineffective because the preceding P wave was blocked and because the underlying rhythm before pacing was 2 1 atrioventricular block The conducted beat inhibited the pacemaker generator as indicated by the broken line in the diagram The last complex is similar to the first one

Fig 4 shows a longer example of the repeating pattern intermittently present in this patient Two paced beats are followed by an unsuccessful stimulus and then by a conducted beat This pattern results from the relative atrial and ventricular rates the demand nature of the pacemaker the 2 1 atrioventricular block and the influence of atrial activity on the pacemaker

Fig 5 presents the analysis of 105 stimuli For P S intervals between 160 and 380 msec 69 per cent of the stimuli were unsuccessful in excitation For P S intervals outside this range 4 per cent of the stimuli were unsuccessful This differ

Table I Synopsis of published cases demonstrating the influence of atrial activity on failing pacemakers

Author & reference	*Range of critical P S intervals (msec)*	*Number of stimuli showing the influence*†	*Type of heart block*	*Type of catheter*	*Proposed mechanism*
Cases in which atrial activity inhibited the stimulus					
Dreifus Fig 11 9	170 300	7	–	–	–
Sanz	280 320	301	A AVB‡	Endo	WI
Preston	100 400	–	A AVB	Endo	ME
Danzig	80-100	14	A AVB	Endo	WI
Abernathy Case 1 (This report)	110 320	42	A AVB	Endo	ME
Abernathy Case 2 (This report)	160 380	33	2 1 AVB	Endo	ME
Cases in which atrial activity facilitated the stimulus					
Soloff Fig 3	50 180	8	None	Epi	–
Igarashi Case 2	140	1	AVB	Endo	WF
Igarashi Case 6	–	–	–	Endo	WF
Igarashi Case 10 Fig 6B	160	1	None	Endo	WF
Arbel Human Case	40 440	7	A AVB	Endo	WF
Arbel Canine Case	10 80	7	None	Epi	WF
Dreifus Fig 11 11	90 200	3	A AVB	–	WF
Fisch	60 110	4	2 1 AVB	–	WF
Dreifus Fig 11 12	100 140	4	–	–	WF
Castellanos Fig 11 (Tracing on Fig 12)	90 100	2	None	–	WF

The P S intervals during which atrial activity exerted its influence on the efficacy of ventricular capture
†The number published in the text of the article or the number obtained by counting from the published electrocardiograms.
‡Symbols and abbreviations A AVB = advanced atrioventricular block AVB = atrioventricular block Endo = endocardial (transvenous) pacing catheter Epi = epicardial (myocardial) pacing catheter ME = mechanical effects P S interval = time interval in msec from the stimulus to onset of preceding P wave WF = Wedensky facilitation WI = Wedensky inhibition The symbol (–) means that the datum was not available in the published report

ence is statistically significant (Chi squared with Yates correction = 47 0 $p < 0\,001$)

A search of the literature yielded 24 additional cases in which atrial activity influenced the efficacy of a failing pacemaker These cases are listed in Table I There are 14 cases in which atrial activity decreased the efficacy of the pacemaker Data obtained from measurements of published electrocardiograms of one of these cases[1] are presented in Fig 6 no clinical details are available For P S intervals between 170 and 300 msec 87 per cent of the stimuli were unsuccessful outside this range of P S intervals none of the stimuli were unsuccessful This difference is statistically significant (Chi squared with Yates correction = 10 9 $p < 0\,001$) The case reported by Sanz and colleagues showed a similar range of critical P S intervals (Table I) In this case there was a fractured endocardial pacing catheter with an abnormally high threshold The inhibition of pacing by atrial activity was present for 5 hours Preston[3] published an abstract describing 11 cases in which the pacing voltage was deliberately set just at the threshold for pacing the P S intervals during which the inhibition occurred were approximately 100 to 400 msec (Preston personal communication) The final case in this group was reported by Danzig and Diamond[4] In this case the critical P S intervals were shorter (80 to 100 msec) than in the other cases described above Of 17 stimuli with P S intervals of 80 to 100 msec three were successful in excitation eight were unsuccessful and six were successful but had a QRS with an unusual appearance Stimuli occurring at other P S interval were successful In Danzig and Diamond's case the inhibition disappeared when the current supplied by the generator was increased

Facilitation of capture by the pacemaker stimulus was observed in nine human and one canine cases (Table I) In this group only Soloff and Fewell[5] described detailed clinical data their patient had an epicardial pacing catheter which had migrated away from the site of initial implantation In the three cases studied by Igarashi and Ayabe[6] the pacemaker current was intentionally set to various low levels before the data were collected In the other five human cases the

clinical data are insufficient to determine if there was malfunction of the pacemaker In the canine experiment of Arbel and co workers [7] the current supplied by the pacemaker was set below the level necessary for completely successful pacing

Inspection of Table I reveals that the critical P S intervals tended to be shorter in those cases where atrial activity facilitated the stimulus as compared to those cases where atrial activity inhibited the stimulus With the exception of the cases of Arbel and colleagues [7] facilitation occurred with P S intervals of 50 to 200 msec and inhibition was associated with P S intervals of 80 to 400 msec In Arbel and colleagues human case although atrial activity favorably influenced ventricular capture during P S intervals of 40 to 440 msec the peak effect was with P S intervals of 100 to 200 msec Arbel and associates canine case is probably not directly comparable to the human cases since the heart rate was relatively fast (160 beats/minute)

In two cases interpreted as facilitation none of the pacemaker stimuli actually failed to excite the heart In one case (1 Fig 11 12) the QRS of the paced beats had an unusual appearance when the stimulus fell within a critical P S interval In the other case ventricular premature beats occurred only following fusion beats (sinus and paced) arising from a critical P S interval.

The type of pacing catheter was reported in 21 of the 26 cases In 19 of the 21 cases there was an endocardial catheter Of the two epicardial catheters one was the malfunctioning catheter described by Soloff and Fewell [3] and the other was used in the canine experiment of Arbel and colleagues

Discussion

The observations presented above indicate that a suitably timed atrial beat can influence a failing pacemaker by facilitating stimuli which are usually unsuccessful in exciting the heart by inhibiting stimuli which are generally successful or by changing the appearance of the QRS of paced beats This influence is exerted by atrial activity which precedes a stimulus by a critical time interval and the values of that interval are uniquely defined for each case The critical P S intervals are shorter (usually 40 to 200 msec) in cases of facilitation than in cases of inhibition (80 to 400 msec) but there is considerable overlap

Pacemaker failure Both of our cases demonstrated overt failure of the pacemaker system (generator and/or catheter) In Case 1 the generator had a depleted cell Whether or not a suboptimally positioned catheter also contributed to the failure is uncertain Proper therapy in Case 1 was replacement of the pacemaker not administration of prednisolone and ephedrine In Case 2 the pacing catheter was malpositioned and repositioning the catheter corrected the problem

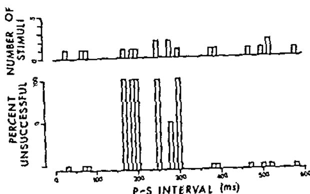


Fig 6 Data for this figure were obtained from a previously published electrocardiogram . *Top* Number of stimuli occurring at each P S interval (defined as in *Fig 2*) *Bottom* Per cent of stimuli that were unsuccessful in ventricular capture for each P S interval.

When the available data from the previously reported cases are examined it is evident that all of the pacemaker systems were failing at the time atrial activity exerted its influence on the efficacy of capture The presence of this phenomenon is an indication for appropriate diagnostic and therapeutic measures to correct the pacemaker failure

Electrotonic mechanism Electrotonic and mechanical mechanisms have been proposed as alternative explanations for the influence of atrial activity Table I indicates the explanations preferred in previous articles A discussion of these mechanisms follows

Wedensky facilitation (as distinguished from the Wedensky effect) is said to occur when an effective stimulus originating above a site of conduction block renders a subthreshold stimulus below the site of block successful in excitation [8, 1, 3] Excitation of the normally conducting cells proximal to the block gives rise to a current which spreads passively through the cells distal to the block (electrotonic current) Facilitation is thought to occur because electrotonic current

from the blocked impulse combines additively with local current from the subthreshold stimulus. Facilitation and summation have been demonstrated by microelectrode studies in canine Purkinje fibers.[14,16] Wedensky inhibition is said to occur when an effective stimulus, originating above a site of conduction block, causes a suprathreshold stimulus below the block to fail in excitation. Cranefield and Hoffman[14] have observed that impulses in depressed canine Purkinje fibers can be inhibited by previous stimulation of other anastomosing fibers. They have suggested[17] that, although the basis of Wedensky inhibition remains unclear, these observations may be the mechanism of Wedensky inhibition.

An electrotonic mechanism (Wedensky facilitation or inhibition) has been favored by nearly all previous authors as the explanation for the influence of atrial activity on ventricular capture by failing pacemakers (Table I). This mechanism requires that current derived from atrial excitation (the P wave) traverse an area of conduction block and exert an electrotonic effect near the tip of the pacing catheter. Electrotonic spread can be expected to extend for at most a few millimeters beyond the site of block because the space constant of the conducting tissue is short.[18] Thus there are only two conditions under which the Wedensky phenomena could have operated in these cases. First, if the pacemaker stimulus gave rise to a fusion beat, this would naturally imply that the atrial excitation was conducted through the atrioventricular junction and excited the ventricles. The excited ventricular tissue could have electrotonically influenced the pacemaker stimulus. There are five cases[5, 6 (C 10) 7 ( ) 8 9] where at least some of the time atrial systole exerted its influence in the presence of a fusion beat.

Second, if the atrioventricular block were caused by bilateral peripheral bundle branch block, atrial excitation could propagate to the terminal bundle branches. An electrotonic current originating at this point could then influence the efficacy of the pacemaker. There are 2 cases with wide (> 120 msec.) unpaced QRS complexes and atrioventricular block.[2, 6 (C 2)] An electrotonic mechanism could have operated in these cases if there was bilateral peripheral bundle branch block.

However, if the site of the block were *in the* atrioventricular node or His bundle, *the distance* between the site of block and the pacing electrode would be too great for an electrotonic spread to influence the stimulus. Both of our cases had atrioventricular block and narrow (< 120 msec.) QRS complexes in the absence of pacing. In Case 1 these were escape beats and in Case 2 these were conducted beats. There are an additional three cases with narrow unpaced QRS complexes, atrioventricular block, and no fusion beats.[1 (Fig 11 9), 4, 7 (b man c 8)] That the QRS was narrow favors the site of block being in the atrioventricular junction.[19] Hence, in these five cases it is difficult to accept the Wedensky phenomena as being the explanation for the influence of atrial activity.

In summary, of the 12 cases for which there are adequate electrocardiographic data, the Wedensky phenomena theoretically could have operated in seven and probably could *not* have operated in five. (There are 14 cases[1 (Figs 11 11 a d 11 12), 3, 6 (C 5 8)] for which information on either the QRS duration or the atrioventricular conduction was not given.)

Mechanical mechanism. An alternative explanation is that atrial systole causes *motion* of the pacing catheter and/or ventricular myocardium and that this motion alters the efficacy of ventricular capture by increasing or decreasing the *contact* between the catheter electrode and the ventricle. Several previous authors[4, 5, 17, 20] have noted this possibility, but few have favored it (Table I).

Table II lists some electromechanical and mechanical intervals which are relevant to this discussion. (We are unaware of more complete data on the motion of the right atrium and ventricle.) Right atrial motion may begin as soon as 58 msec. after the onset of the P wave. If the right atrial contraction were similar to the left atrial contraction, the right atrial contraction wave could last over 100 msec. (Table II). In terms of the atrial contribution to ventricular motion, experimental studies[1, 24] indicate that a suitably timed atrial systole improves ventricular function in part by augmenting ventricular diastolic volume. Several studies[25, 31] in man have shown that atrial systole favorably affects ventricular performance when the P-R interval ranges between 100 and 400 msec. and that the maximum effect occurs with P-R intervals of approximately 150 to 300 msec. Moreover, studies with the apexcardiogram in man (Table II) have demonstrated that atrial systole causes diastolic ventricular motion which may begin as soon as 80

msec after the P wave and which may continue for over 300 msec after the onset of the P wave

These observations suggest two ways in which atrial systole may influence a pacemaker stimulus First atrial contraction may move the pacing catheter if part of the catheter is in intimate contact with the atrial wall This movement could push the catheter closer to the ventricular wall thus enhancing the efficacy of capture However in the presence of a broken catheter lead this motion could separate the broken ends through twisting or bending of the catheter apparent inhibition of the pacemaker stimulus would result Second atrial systole could move the ventricular wall relative to the catheter This movement would be caused by an expanding ventricular diastolic volume and would occur 100 to 400 msec after the onset of the P wave This ventricular motion could increase or decrease the contact between the pacing electrode and the endocardium with subsequent changes in the efficacy of capture

Sanz and associates rejected a mechanical mechanism because they thought that the effects of atrial systole would not last more than 200 msec after the onset of the P wave In our opinion this objection is invalid since our review has shown that atrial systole can influence ventricular motion up to 400 msec after the P wave Igarashi and Ayabe[illegible] state that the observation[illegible] of facilitation with epicardial electrodes is incompatible with a mechanical mechanism For reasons outlined in another report [illegible] we do not agree with this objection

Because right atrial and ventricular hemodynamics have not been investigated as fully as those on the left side we are unable to state conclusively that in man atrial systole can mechanically influence a pacing catheter as described above However we think the probability is high that right atrial systole exerts mechanical effects sufficient to explain most if not all of the cases under consideration This supposition is strengthened by the report of Preston [illegible] who radiographically observed movement of the pacing catheter related to atrial systole in eight patients. Moreover recent experimental work provides additional support for the mechanical explanation The mechanical mechanism has the advantages of being relatively simple conceptually of being a single mechanism for the diverse changes in pacing function related to atrial systole and of being independent of the presence or site of atrioventricular block

Table II Electromechanical and mechanical intervals involving atrial systole

Interval	*Time (msec)*	*Reference*
Onset of P wave to onset of right atrial systole	58-72	34
Onset of P wave to onset of left atrial systole	76-94	34
Onset to peak of left atrial contraction wa e		
Normal subjects	30-80 average 55	35
Diseased subjects	50-140 average 87	35
Onset of P wave to A wave of apexcardiogram	120-1[illegible]0 average 140	36
	80-160 average 110	37
	80-120	38
Duration of A wave of apexcardiogram		
Normal subjects	20-50	38
	30-130 average 60	39
Diseased subjects	40-260 average 90	39

Summary

Atrial activity can influence the ability of a failing artificial pacemaker to excite the heart An appropriately timed atrial beat may cause failure in excitation by pacemaker stimuli which are usually successful in ventricular capture Conversely stimuli which usually fail in excitation may be made to succeed by an appropriately timed atrial beat Two case reports and a review of the literature are presented Alternative mechanisms for this influence of atrial activity are electrotonic effects (Wedensky facilitation or inhibition) and mechanical effects (motion of the pacing catheter or ventricular myocardium) The authors consider the latter mechanism preferable

We wish to thank Dr Thomas A Preston who provided the material for Case 1 and Dr Arthur B Simon who gave us permission to use the material for Case 2

Addendum

After this manuscript was prepared an article appeared with additional examples of the influence of atrial systole on pacemaker capture (Goldberg E Mechanical factors and the elec

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Clinical pathologic conference

A discussion on hypertrophic cardiomyopathy

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Barry J Maron M D
Andrew G Morrow M D
Stephen E Epstein M D
William C Roberts M D
Bethesda Md

DR. ROBERTS The purpose of this conference is to discuss certain clinical operative and morphologic features of hypertrophic cardiomyopathy as exemplified in one patient Dr Spray will present the patient

DR SPRAY R H (11 65 60-4) a 56-year old white woman was not suspected of having heart disease until she was 30 years old when a precordial murmur was heard She was in good health until age 40 when she developed angina pectoris and palpitations From age 51 on her symptoms increased in frequency and severity In addition she developed orthopnea and paroxysmal nocturnal dyspnea During the year before death occasional syncopal and presyncopal episodes occurred In February 1976 she was admitted to a local hospital where an electrocardiogram showed left ventricular hypertrophy with the strain pattern A treadmill exercise tolerance test was attempted but it was stopped when she developed paroxysmal atrial tachycardia Cardiac catheterization disclosed the following pressures (in mm Hg) right ventricle (body) 50/3 right ventricle (subpulmonic area) 21/3 pulmonary trunk 21/17 (mean 12) pulmonary arterial wedge mean 7 left ventricle (body) 235/0-25 left ventricle (subaortic area) 105/12 and aorta 105/60 (mean 80) The peak systolic pressure gradient between left ventricle and aorta was 130 mm Hg The cardiac output was 4 7 liters per minute and the cardiac index 3 0 liters/minute/M^2 She was begun on propranolol (160 mg per day) and quinidine

In May 1976 she was admitted to a local hospital for treatment of severe headache at which time diastolic blood pressures to 130 mm Hg were noted Diazoxide therapy resulted in marked hypotension which required intravenous metaraminol for stabilization She was admitted to the National Heart Lung and Blood Institute 19 days before death

On examination the blood pressure was 120/80 mm Hg heart rate 56 per minute and respiratory rate 12 per minute The jugular venous pulse was normal The carotid arterial upstroke was judged to be rapid The lung fields were clear to auscultation The point of maximal cardiac impulse was in the sixth left intercostal space in the anterior axillary line and the apical beat had a triple character The first and second heart sounds were normal a fourth heart sound was present at the apex A Grade 4/6 systolic ejection type murmur was heard loudest at the apex and it radiated to the base The murmur increased in intensity on standing but did not change with Valsalva maneuver Neither liver nor spleen were palpated but mild pedal edema was noted

DR ROBERTS Dr Maron could you describe the electrocardiogram chest roentgenogram and echocardiogram

DR MARON The *electrocardiogram* shows left ventricular hypertrophy with strain pattern (Fig 1) In addition the T waves in Leads I and aV_L are deeply inverted in a symmetric fashion ST segments are elevated in Leads V_1 and V_2 and depressed in Leads V_5 and V_6 Left atrial enlargement also is evident The *chest radiograph* shows pectus excavatum left ventricular enlargement

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trocardiogram, AM HEART J 93 629, 1977) Figs 5 through 9 in that article illustrate several clinical cases In one case, fluoroscopy confirmed movement of the pacing catheter induced by atrial systole

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Clinical pathologic conference

A discussion on hypertrophic cardiomyopathy

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DR ROBERTS The purpose of this conference is to discuss certain clinical operative and morphologic features of hypertrophic cardiomyopathy as exemplified in one patient Dr Spray will present the patient

DR SPRAY R H (11 65 60-4) a 56 year old white woman was not suspected of having heart disease until she was 30 years old when a precordial murmur was heard She was in good health until age 40 when she developed angina pectoris and palpitations From age 51 on her symptoms increased in frequency and severity In addition she developed orthopnea and paroxysmal nocturnal dyspnea During the year before death occasional syncopal and presyncopal episodes occurred In February 1976 she was admitted to a local hospital where an electrocardiogram showed left ventricular hypertrophy with the strain pattern A treadmill exercise tolerance test was attempted but it was stopped when she developed paroxysmal atrial tachycardia Cardiac catheterization disclosed the following pressures (in mm Hg) right ventricle (body) 50/3 right ventricle (subpulmonic area) 21/3 pulmonary trunk 21/17 (mean 12) pulmonary arterial wedge mean 7 left ventricle (body) 235/0 25 left ventricle (subaortic area) 105/12 and aorta 105/60 (mean 80) The peak systolic pressure gradient between left ventricle and aorta was 130 mm Hg The cardiac output was 4 7 liters per minute and the cardiac index 3 0 liters/minute/M She was begun on propranolol (160 mg per day) and quinidine

In May 1976 she was admitted to a local hospital for treatment of severe headache at which time diastolic blood pressures to 130 mm Hg were noted Diazoxide therapy resulted in marked hypotension which required intravenous metaraminol for stabilization She was admitted to the National Heart Lung and Blood Institute 19 days before death

On examination the blood pressure was 120/80 mm Hg heart rate 56 per minute and respiratory rate 12 per minute The jugular venous pulse was normal The carotid arterial upstroke was judged to be rapid The lung fields were clear to auscultation The point of maximal cardiac impulse was in the sixth left intercostal space in the anterior axillary line and the apical beat had a triple character The first and second heart sounds were normal a fourth heart sound was present at the apex A Grade 4/6 systolic ejection type murmur was heard loudest at the apex and it radiated to the base The murmur increased in intensity on standing but did not change with Valsalva maneuver Neither liver nor spleen were palpated but mild pedal edema was noted

DR ROBERTS Dr Maron could you describe the electrocardiogram chest roentgenogram and echocardiogram

DR MARON The *electrocardiogram* shows left ventricular hypertrophy with strain pattern (Fig 1) In addition the T waves in Leads I and aV_L are deeply inverted in a symmetric fashion ST segments are elevated in Leads V_1 and V_2 and depressed in Leads V_5 and V_6 Left atrial enlargement also is evident The *chest radiograph* shows pectus excavatum left ventricular enlargement

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trocardiogram, AM HEART J 93 629, 1977) Figs 5 through 9 in that article illustrate several clinical cases In one case, fluoroscopy confirmed movement of the pacing catheter induced by atrial systole

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was noted and no systolic thrill was palpated in the right ventricle at the end of the procedure The patient came off bypass easily

DR ROBERTS Dr Morrow *what occurred in the postoperative period?*

DR MORROW The patient was hemodynamically stable throughout the first postoperative day and the first postoperative electrocardiogram showed sinus rhythm and a left bundle branch block pattern The latter is very common after this operation On the first postoperative day however she developed junctional bradycardia and she was paced via a temporary pacemaker wire which had been implanted at operation Supraventricular and junctional tachyarrhyth mias followed but ultimately sinus rhythm returned No electrocardiographic changes suggestive of acute myocardial infarct occurred Because of the supraventricular irritability propranolol was reinstituted On the following day a new precordial murmur with an accompanying thrill was noted at the apex and left sternal border It was holosystolic and Grade 4/6 in intensity On the following day her ventricular rate suddenly decreased to less than 40 beats per minute The pacemaker failed to capture the ventricle and she died

DR. ROBERTS Dr Spray could you describe the *findings at necropsy*

DR SPRAY At necropsy the heart weighed 680 grams (Figs 5 and 6) (The patient weighed 54 5 kilograms) Considerable hemorrhage was present in the atrial septum The tricuspid valve was normal except that its anterior leaflet appeared more elongated than usual The wall of the right *ventricle measured up to 1 3 cm in thickness* The pulmonic valve was normal Both atria were quite dilated Both mitral valve leaflets were thickened by fibrous tissue The left ventricular cavity was small Measurements of the thickness of the left ventricular myocardium were made at the level at which the ultrasound beam would theoretically pass during life i e between the papillary muscles at the level of the distal margins of the mitral leaflets and at the midpoint of the posterior mitral leaflet At this level (the echo area) the ventricular septum measured 25 mm and the posterobasal left ventricular free wall 25 mm in maximal thickness The posterobasal portion of left ventricular free wall was thick and rounded typical of the configuration observed in patients with left ventricular outflow obstruction at rest

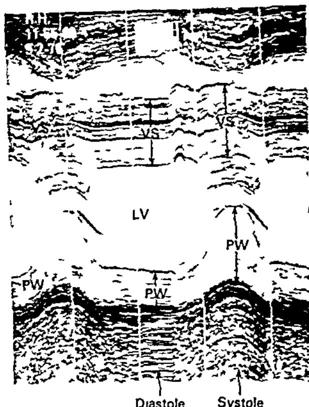


Fig 3 Echocardiogram of present patient showing disproportionate thickening of the ventricular septum *(VS)* with respect to the posterobasal left ventricular wall *(PW)* in diastole In contrast concentric ventricular wall thickening is present in systole *LV* = left ventricular cavity

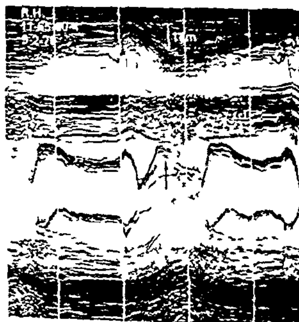


Fig 4 Echocardiogram of present patient showing systolic anterior motion of the anterior mitral leafl t (arrow)

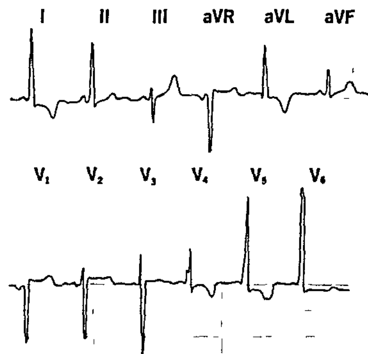


Fig 1 Preoperative electrocardiogram of present patient showing left ventricular hypertrophy with strain pattern left atrial enlargement and ST segment and T wave abnormalities



Fig 2 Posteroanterior chest radiograph in present patient showing mild cardiac enlargement and normal pulmonary vascular markings

and normal pulmonary vascular markings (Fig 2) *Echocardiogram* shows (in diastole) ventricular septal thickness of 24 mm posterobasal left ventricular wall thickness of 16 mm, and a septal to free wall ratio of 1 5 When wall thicknesses are measured in systole however, the ventricular septum is 26 mm the posterobasal left ventricular wall is 29 mm, and hence, the septal to free wall ratio in systole is 0 9 (Fig 3) In addition marked systolic anterior motion of the anterior mitral leaflet, indicative of severe obstruction to left ventricular outflow, is evident (Fig 4) The transverse internal dimensions of the left ventricular (43 mm) and left atrial (38 mm) cavities and the aortic root (32 mm) were within normal limits

Dr Roberts Dr Epstein what were your *reasons for recommending operation* in this patient

Dr Epstein This patient was considered an ideal candidate for septal myotomy-myectomy for the following reasons (1) she was severely limited (New York Heart Association, Functional Class III) by extreme fatigue and dyspnea with exertion and in addition she had numerous episodes of syncope and lightheadedness, (2) these symptoms were not lessened significantly by treatment with propranolol (3) a marked (130 mm Hg) peak systolic pressure gradient was present in the left ventricular outflow tract under basal conditions (4) there was evidence by echo cardiography of a markedly thickened ventricular septum that would permit an adequate myectomy to be performed, and (5) no other major medical problems were identified that would contraindicate a major cardiac operation

Dr Roberts Dr Morrow could you *describe what you found at operation* in this patient and the operative procedure you performed

Dr Morrow The operation performed was the ventricular myotomy and myectomy which has been used in this institution with minor modifications for 17 years [1] With the patient on cardiopulmonary bypass the aorta was opened After gently retracting the aortic valve cusps the thickened ventricular septum was observed Two longitudinal parallel incisions were made in the ventricular septum The incisions extended caudally from just below the commissure between the right and left aortic valve cusps. The incisions were then joined transversely and the resulting wedge of myocardium was excised After this procedure the ventricular septum was palpated and noted to be somewhat thinner than in most patients after this operation The aortotomy incision was closed No aortic regurgitation

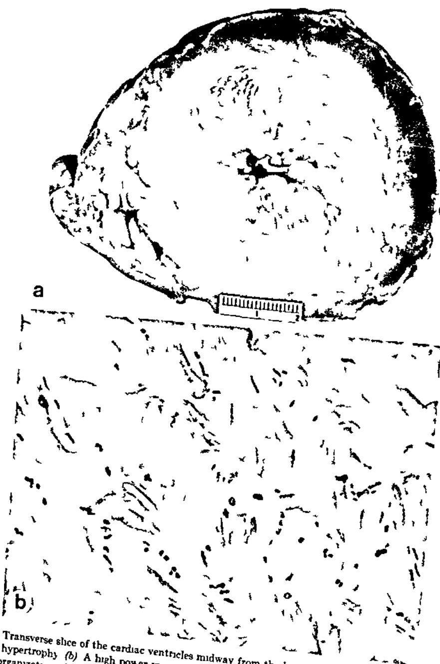


Fig 6 *(a)* Transverse slice of the cardiac ventricles midway from the base to the apex showing concentric left ventricular hypertrophy *(b)* A high power view of a portion of myocardium from ventricular septum showing marked disorganization of cells and myofibrillar elements (Hematoxylin and eosin stain original magnification ×330)

The myocardium adjacent to the site where the drain was inserted at operation in the apex of left ventricle was necrotic The edges of the area of operatively excised ventricular septum were necrotic The most cephalad aspect of this excision extended all the way through the ventricular septum creating a slit like ventricular septal defect 1 cm long There were no areas of myocardial fibrosis The aortic valve was normal anatomically The epicardial coronary arteries were grossly normal Histologic examination of the left ventricular septum showed marked disor

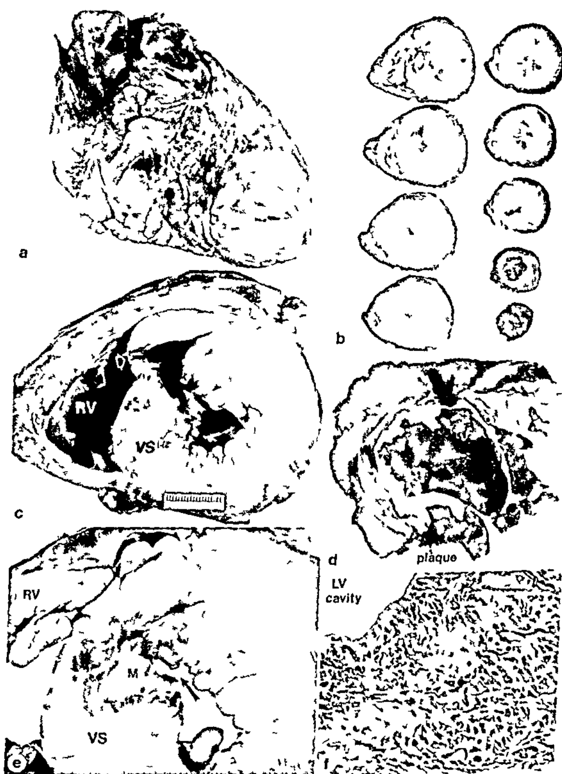


Fig 5 a through f (a) Anterior view of the heart at necropsy showing marked left ventricular prominence (b) Serial slices of the cardiac ventricles from base to apex showing severe left ventricular hypertrophy Hemorrhagic necrosis is present in the apical slices due to its being the site of insertion of the left ventricular drain at operation (c) View of the base of the heart from below showing the area of excision of muscle (arrow) from the left ventricular septum (VS) The site of rupture of the septum with creation of a ventricular septal defect (arrow) is shown RV = right ventricle (d) The left ventricular septal muscle excised at operation showing an endocardial fibrous plaque consistent with a contact lesion from the anterior mitral leaflet The excised muscle weighed 4 1 grams (e) Close up of a basal slice of the cardiac ventricles showing the myectomy site (arrow) and the surrounding area of necrosis (M) (f) Histologic section of an area of VS adjacent to the myectomy incision showing marked disorganization of myocardial cells and necrosis (Hematoxylin and eosin stain original magnification ×80)

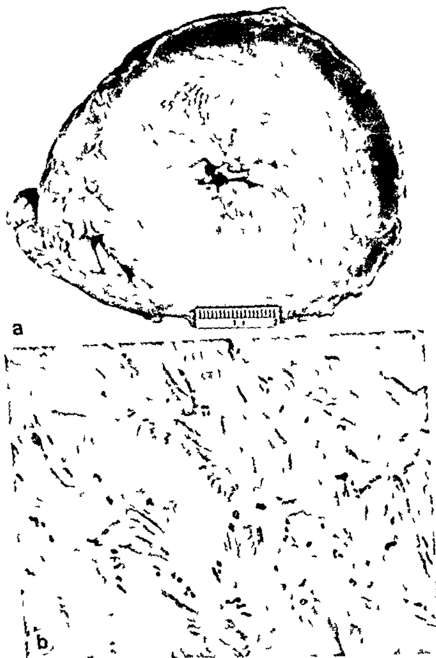


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ganization of myocardial fibers and coagulation necrosis of myocardium bordering the myotomy and myectomy incision (*Figs 5 and 6*) The intramural coronary arteries in the ventricular septum were normal

DR ROBERTS Dr Epstein patients with hypertrophic cardiomyopathy often have *chest pain* occasionally clear angina pectoris just like patients with valvular aortic stenosis What is the cause of angina pectoris in patients with hypertrophic cardiomyopathy? Do they have associated coronary arterial narrowing due to atherosclerosis or is there another cause for the angina pectoris? Or is it really angina pectoris?

DR EPSTEIN It is true that many patients with hypertrophic cardiomyopathy or ASH, have chest pain or discomfort indistinguishable from that of typical angina pectoris Since coronary artery disease is relatively common it is not surprising to find that the two diseases occasionally coexist in a given patient In such patients the coronary artery disease undoubtedly contributes to the chest pain syndrome However, in the large majority of patients with hypertrophic cardiomyopathy chest discomfort occurs without any coronary arterial abnormality discernible by coronary angiography or at necropsy In patients with obstruction to left ventricular outflow (who consequently have high intraventricular pressures) angina probably occurs because of the excessively high myocardial oxygen consumption, i e , myocardial oxygen demands outstrip the capacity of the coronary arteries to deliver oxygen just as in patients with aortic stenosis In patients without obstruction the origin of the patient s chest pain is unclear It may be that proliferation of myocardial capillaries has not kept pace with the excessive amount of hypertrophy present in these patients

DR ROBERTS Dr Epstein what is the cause of *syncope or presyncope* in patients with hypertrophic cardiomyopathy? Is syncope more frequent in the patients with obstruction to left ventricular outflow at rest or is it just as frequent in patients without obstruction either at rest or with provocation?

DR EPSTEIN Syncope and presyncope occur commonly in patients with obstruction to left ventricular outflow as well as in patients without obstruction to left ventricular outflow This fact suggests that while syncope in patients with hypertrophic cardiomyopathy may be due to an abrupt increase in the magnitude of left ventricular outflow obstruction in some patients other mechanisms also must be operative One such mechanism that can lead to syncope and presyncope in patients with hypertrophic cardiomyopathy is a ventricular arrhythmia Supportive evidence for this conclusion is the documentation of ventricular fibrillation just after collapse in a few patients observed by us and other investigators It should also be emphasized that although syncope and presyncope are common in patients with obstructive hypertrophic cardiomyopathy these symptoms do not have the same alarming connotation in such patients as they would in patients with fixed valvular aortic stenosis We have for example, followed many patients for over 10 years with such symptoms Such a benign course would be unheard of in a patient with syncope associated with valvular aortic stenosis Hence, we do not recommend operation to relieve obstruction in patients with hypertrophic cardiomyopathy on the basis of syncope or presyncope alone On the other hand, we have evaluated some patients who have died suddenly with no symptomatology before death other than a single episode of syncope or occasional presyncope Hence it is possible that syncope can be the first manifestation of cardiac disease before sudden death in patients with hypertrophic cardiomyopathy

DR ROBERTS Dr Epstein, I understand a number of patients with hypertrophic cardiomyopathy with or without obstruction have *exertional dyspnea* How many patients with this condition actually have overt evidence of *congestive heart failure* or to put it another way is congestive heart failure in the patient with hypertrophic cardiomyopathy similar to congestive heart failure in patients with other cardiac conditions? Morphologically hypertrophic cardiomyopathy is one of the conditions in which congestive heart failure occurs and yet, neither ventricular cavity is dilated Among the few conditions in which congestive cardiac failure occurs and the ventricular cavities are not dilated are amyloidosis mitral stenosis hemochromatosis and constrictive pericarditis Is there anything different clinically about the congestive heart failure in patients with hypertrophic cardiomyopathy compared to that occurring in patients with other cardiac conditions?

DR EPSTEIN Patients with hypertrophic cardio

myopathy may demonstrate many of the clinical manifestations we interpret as indicative of congestive heart failure The mechanism of failure however is probably different in this condition than in patients with acquired valvular heart disease for example Patients with hypertrophic cardiomyopathy have a poorly compliant left ventricle This is due presumably to the markedly thickened ventricular walls This stiffened ventricle results in restriction to left ventricular filling i.e left ventricular inflow obstruction As a result left atrial and pulmonary venous pressures increase and consequently may lead to clinical manifestations of left and right sided heart failure This occurs despite preservation of systolic function at least as assessed at rest Many patients with either the obstructive or the non obstructive form of the disease may manifest these findings In fact in the latter stages of non obstructive hypertrophic cariomyopathy patients may present with a picture very similar to that of congestive or dilated cardiomyopathy with the exception that the ventricular cavities do not dilate On the other hand (1) we and others have observed a small number of patients with non obstructive hypertrophic cardiomyopathy who in the end stages of their disease manifest impaired systolic function (normal end diastolic volume with decreased ejection fraction) and (2) a very few patients have shown mild enlargement of the left ventricular cavity in end-diastole The most characteristic picture of end-stage disease in non obstructive hypertrophic cardiomyopathy however is inflow obstruction with normal left ventricular end diastolic volume and preservation of systolic function

DR ROBERTS The present patient had historical evidence of *systemic hypertension* on one or more occasions although the blood pressure recordings at NIH were normal Dr Maron how often does systemic hypertension occur in patients with hypertrophic cardiomyopathy and how often do patients with systemic hypertension have *echo*cardiographic or morphologic evidence of hypertrophic cardiomyopathy?

DR MARON One of the first concepts of hypertrophic cardiomyopathy was that the subaortic muscular stenosis was due to preexisting systemic hypertension probably because some of the first patients described with this condition nearly 20 years ago just happened to have coexistent systemic hypertension Subsequently we have come to realize that hypertension is not common in patients with hypertrophic cardiomyopathy Hence there is very little evidence for a causal relation between the two conditions Looking at this question in another way we have studied by echocardiography and at necropsy over 300 patients with systemic hypertension and found disproportionate septal thickening in about 5 per cent Furthermore the disporportionate septal thickening in patients with systemic hypertension does not appear to be genetically transmitted but rather secondary to the patient s particular hemodynamic state—i e systemic hypertension Hence systemic hypertension is uncommon in patients with hypertrophic cardiomyopathy and disproportionate septal thickening is uncommon in patients with systemic hypertension

DR ROBERTS The present patient had a loud *precordial murmur* and most *patients with* hypertrophic cardiomyopathy I understand have a precordial murmur Dr Maron do any patients with hypertrophic cardiomyopathy not have a murmur and when a murmur is present what is it due to?

DR MARON *Actually in our experience* loud precordial murmurs are rare in the over all population of patients whom we see with hypertrophic *cardiomyopathy* This is due principally to the fact that about 75 per cent of the patients who we *evaluate with this* condition do *not* have obstruction to left ventricular outflow If outflow obstruction is absent then a loud murmur (Grade 3/6 or more) rarely if ever is present In patients with obstruction to left ventricular outflow (such as the patient discussed here) a loud systolic ejection murmur is almost invariably present along the left sternal border and at the apex These statements however have to be tempered by the fact that the left ventricular outflow gradient in hypertrophic cardiomyopathy is extremely labile and may be present or absent from beat to beat hour to hour *or day to day* Therefore the presence or absence of a precordial murmur or its intensity at *any one* point in time cannot be used as definitive evidence of obstruction to outflow

DR ROBERTS Thus a patient with a loud precordial systolic murmur and hypertrophic cardiomyopathy with rare exception has obstruction to left ventricular outflow What happens to the systolic *precordial murmur after adequate myotomy or myectomy?*

DR MARON The precordial murmur in patients with hypertrophic cardiomyopathy is mainly related to systolic anterior motion of the mitral valve, which results in outflow obstruction and often mitral regurgitation Since myotomy-myectomy almost invariably obliterates the resting gradient in these patients, the murmur either disappears or is markedly diminished in intensity

DR ROBERTS Although a few patients with hypertrophic cardiomyopathy have obstruction not only to left ventricular outflow but also to right ventricular outflow, I wonder, Dr Maron, what the explanation for the right ventricular outflow obstruction really is For example, I am not aware that the ventricular septum is any thicker in patients with right ventricular outflow obstruction than in patients with no obstruction to right ventricular outflow but considerable left ventricular outflow obstruction Why is not the right ventricular outflow obstruction more common and what is your explanation for the obstruction when it does occur?

DR MARON About 20 per cent of our patients with hypertrophic cardiomyopathy and obstruction to left ventricular outflow also have right ventricular outflow tract gradients (usually less than 40 mm Hg) However, a rare patient manifests marked obstruction to right ventricular outflow which is occasionally greater than, or present in the absence of, obstruction to left ventricular outflow Although the explanation for right ventricular outflow gradients in patients with hypertrophic cardiomyopathy is unclear, it is perhaps most likely that the markedly hypertrophied ventricular septum and/or crista supraventricularis impinges on the right ventricular outflow tract and produces obstruction

DR ROBERTS We have studied 65 patients with hypertrophic cardiomyopathy at necropsy and as I recall only three had obstruction to right ventricular outflow and the largest gradient among the three was 50 mm Hg In that particular patient the anterior tricuspid valve leaflet was quite elongated, and it appeared possible that the excessive length of the anterior tricuspid valve leaflet located in a small right ventricular cavity was the likely explanation for the obstruction In the present patient the right ventricular outflow gradient was 29 mm Hg and the anterior tricuspid valve leaflet probably was more elongated than normal The present patient also had a very thick crista supraventricularis and an extremely small right ventricular cavity At necropsy, for example (Figs 5 and 6) the right ventricular free wall virtually contacts the right ventricular aspect of the ventricular septum.

Dr Maron there appears to be some discrepancy between the thicknesses of the ventricular walls measured at necropsy and during life by echocardiography in this patient. Can you explain these discrepancies?

DR MARON Recently we have observed several patients with hypertrophic cardiomyopathy similar in this respect to the patient described in this report[2] That is the echocardiogram during life showed asymmetric septal hypertrophy but at necropsy concentric hypertrophy was present In this patient, the echocardiogram showed a septal to free wall ratio of 1 5 in diastole, which met our diagnostic criteria of ASH However, at necropsy the septal to free wall ratio was 0 9 and therefore not diagnostic of ASH These discrepancies may be explained as follows First, in patients with ASH, the ventricular septum thickens less during ventricular systole than does the left ventricular free wall As a result, septal to free wall ratios are greater when measurements are obtained in diastole than when they are obtained in systole Second hearts examined at necropsy appear to be in the systolic phase of the cardiac cycle This conclusion is suggested by the fact that the ventricular wall thickness septal to free wall ratios and left ventricular internal transverse dimensions measured at necropsy all correlated more closely with measurements attained echocardiographically in systole than in diastole[7] Since by convention, echocardiographic measurements of wall thicknesses are made during diastole it becomes clear why septal to free wall ratios consistent with the diagnosis of hypertrophic cardiomyopathy (ASH) during life may be inconsistent with this diagnosis after death Hence, we believe that at least occasionally echocardiographic measurements in diastole provide a more sensitive method than necropsy examination for documenting the presence of hypertrophic cardiomyopathy

The implication of these findings is that in certain patients with typical genetically transmitted hypertrophic cardiomyopathy, the diagnosis will not be established at necropsy by simple measurement of the relative thicknesses of the ventricular septum and left ventricular free wall

In such patients the correct diagnosis will rely on other ancillary observations including typical hemodynamic and echocardiographic features of left ventricular outflow obstruction during life (as shown in the present patient) and the presence of a documented family history of hypertrophic cardiomyopathy Other necropsy findings suggestive but not diagnostic of hypertrophic cardiomyopathy include a contact plaque on the endocardium of the ventricular septum in apposition to a thickened anterior mitral leaflet and the presence of numerous hypertrophied and disorganized cardiac muscle cells in the ventricular septum

DR ROBERTS Dr Maron on the echocardiographic record are you always sure about the exact location of the epicardial surface of the posterior left ventricular free wall in patients with hypertrophic cardiomyopathy? I would assume that you would be considerably pleased if patients with hypertrophic cardiomyopathy had a little pericardial effusion so that this surface of the free wall would be clearly delineated Could you comment on how often you feel that you cannot make a precise unequivocal measurement of the posterior free wall by echocardiogram in patients with hypertrophic cardiomyopathy

DR MARON Dr Roberts comments about technical considerations in obtaining optimal echocardiograms is certainly well taken A satisfactory echocardiogram can probably be obtained in 80 to 90 per cent of patients with hypertrophic cardiomyopathy Nevertheless there are some important technical points that should always be considered For example delineation of the right ventricular surface of the ventricular septum itself is often very difficult in some patients Furthermore as Dr Roberts has pointed out measurement of the posterobasal left ventricular wall is also frequently difficult in these patients with regard to definition of either the endocardial or epicardial surface In a small minority of patients with clinically evident hypertrophic cardiomyopathy it has not been possible to make a definitive conclusion about the septal to free wall ratio because of these considerations

DR ROBERTS Dr Morrow your results with myotomy and myectomy in patients with hypertrophic cardiomyopathy have been quite gratifying with few exceptions The present patient obviously is one of those exceptions I understand that you have operated on nearly 200 patients with hypertrophic cardiomyopathy and that the occurrence of a ventricular septal defect has been quite rare I wonder if you could comment on your general results with this procedure and your views on the particular operative complications in this particular patient

DR MORROW I have now operated upon approximately 175 patients with the obstructive form of hypertrophic subaortic stenosis The operative mortality rate associated with the procedure is similar to that for aortic valve replacement i e 5 to 7 per cent We have had relatively few late deaths due to heart disease and as yet I do not think we can make meaningful comparisons of the natural histories of operated and unoperated patients Among operative survivors symptomatic improvement has been quite satisfactory nearly two thirds of patients consider themselves asymptomatic and the others with few exceptions are in Functional Class II Ventricular septal defects have occurred in a total of seven patients Several of them were created and recognized at the time of operation but it was not considered necessary to close them One of these patients subsequently had to have the defect closed because he developed heart failure In the remaining patients including the patient being discussed here the ventricular septum ruptured after operation as a consequence of septal infarction I assume that infarction occurred in these patients because the muscular resection was too extensive and compromised the blood supply of the septum beneath and adjacent to it We have recently found that intraoperative measurements of the thickness of the septum by means of an intracardiac echo transducer are of aid in gauging the extent of resection necessary

DR ROBERTS In the present patient 4 1 Gm of ventricular septum was excised at operation Dr Spray in the other patients in whom this procedure has been performed by Dr Morrow how many grams of myocardium were excised from ventricular septum?

DR SPRAY Among 75 specimens the excised muscle ranged in weight from 0 2 to 6.8 grams (average 1 8 Gm)

DR ROBERTS One other anatomic feature of hypertrophic cardiomyopathy is the presence of wall thickening and luminal narrowing of intramural coronary arteries located primarily in the ventricular septum but also occasionally in right ventricular and left ventricular free walls These

DR MARON The precordial murmur in patients with hypertrophic cardiomyopathy is mainly related to systolic anterior motion of the mitral valve, which results in outflow obstruction and often mitral regurgitation. Since myotomy-myectomy almost invariably obliterates the resting gradient in these patients the murmur either disappears or is markedly diminished in intensity.

DR ROBERTS Although a few patients with hypertrophic cardiomyopathy have obstruction not only to left ventricular outflow but also to right ventricular outflow I wonder, Dr Maron, what the explanation for the *right ventricular outflow obstruction* really is. For example, I am not aware that the ventricular septum is any thicker in patients with right ventricular outflow obstruction than in patients with no obstruction to right ventricular outflow but considerable left ventricular outflow obstruction. Why is not the right ventricular outflow obstruction more common and what is your explanation for the obstruction when it does occur?

DR MARON About 20 per cent of our patients with hypertrophic cardiomyopathy and obstruction to left ventricular outflow also have right ventricular outflow tract gradients (usually less than 40 mm Hg). However, a rare patient manifests marked obstruction to right ventricular outflow which is occasionally greater than or present in the absence of, obstruction to left ventricular outflow. Although the explanation for right ventricular outflow gradients in patients with hypertrophic cardiomyopathy is unclear it is perhaps most likely that the markedly hypertrophied ventricular septum and/or crista supraventricularis impinges on the right ventricular outflow tract and produces obstruction.

DR ROBERTS We have studied 65 patients with hypertrophic cardiomyopathy at necropsy and as I recall only three had obstruction to right ventricular outflow and the largest gradient among the three was 50 mm Hg. In that particular patient the anterior tricuspid valve leaflet was quite elongated, and it appeared possible that the excessive length of the anterior tricuspid valve leaflet located in a small right ventricular cavity was the likely explanation for the obstruction. In the present patient, the right ventricular outflow gradient was 29 mm Hg and the anterior tricuspid valve leaflet probably was more elongated than normal. The present patient also had a very thick crista supraventricularis and an extremely small right ventricular cavity. At necropsy, for example (Figs 5 and 6) the right ventricular free wall virtually contacts the right ventricular aspect of the ventricular septum.

Dr Maron, there appears to be some *discrepancy between the thicknesses of the ventricular walls measured at necropsy and during life by echocardiography* in this patient. Can you explain these discrepancies?

DR MARON Recently, we have observed several patients with hypertrophic cardiomyopathy similar in this respect to the patient described in this report.[2] That is, the echocardiogram during life showed asymmetric septal hypertrophy but at necropsy concentric hypertrophy was present. In this patient, the echocardiogram showed a septal to free wall ratio of 1 5 in diastole, which met our diagnostic criteria of ASH. However, at necropsy the septal to free wall ratio was 0 9 and therefore not diagnostic of ASH. These discrepancies may be explained as follows. First in patients with ASH the ventricular septum thickens less during ventricular systole than does the left ventricular free wall. As a result, septal to free wall ratios are greater when measurements are obtained in diastole than when they are obtained in systole. Second, hearts examined at necropsy appear to be in the systolic phase of the cardiac cycle. This conclusion is suggested by the fact that the ventricular wall thickness, septal to free wall ratios and left ventricular internal transverse dimensions measured at necropsy all correlated more closely with measurements attained echocardiographically in systole than in diastole.[2] Since by convention echocardiographic measurements of wall thicknesses are made during diastole, it becomes clear why septal to free wall ratios consistent with the diagnosis of hypertrophic cardiomyopathy (ASH) during life may be inconsistent with this diagnosis after death. Hence we believe that at least occasionally echocardiographic measurements in diastole provide a more sensitive method than necropsy examination for documenting the presence of hypertrophic cardiomyopathy.

The implication of these findings is that in certain patients with typical genetically transmitted hypertrophic cardiomyopathy, the diagnosis will not be established at necropsy by simple measurement of the relative thicknesses of the ventricular septum and left ventricular free wall.

Creatine kinase isoenzymes in the assessment of heart disease

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Because chest pain and transitory electrocardiographic changes do not differentiate patients with coronary insufficiency from those with myocardial infarction objective confirmation of myocardial necrosis by analysis of plasma enzymes has assumed increasing importance Enzymes such as serum glutamic oxalacetic transaminase (SGOT) lactate dehydrogenase (LDH) and creatine kinase (CK)* may be released into blood from organs besides the heart However delineation of isoenzyme profiles improves diagnostic specificity substantially Since elevated plasma activity of one isoenzyme of CK MB CK appears to be the most sensitive and specific enzymatic index of acute myocardial infarction [2,3] MB CK will be the subject of this selective review

Characteristics of creatine kinase and creatine kinase isoenzymes

Creatine kinase is a dimeric molecule with molecular weight of approximately 86 000 daltons consisting of two subunits of either the B or M type The M subunit is predominant in skeletal muscle the B subunit in brain CK participates in a reversible reaction transferring high energy phosphate from ATP to creatine phosphate Arginine in each monomer binds the magnesium ATP or ADP complex necessary for the reaction Each monomer contains one sulfhydryl group necessary for enzymatic activity Thus a thiol activator is needed to elicit maximal activity *in vitro*[5] CK dimers are subject to dissociation into subunits particularly when exposed to freezing and thawing or to high concentrations of urea

Three CK isoenzymes have been recognized in plasma BB MM and MB Because of the negative charge of the B subunit at pH 8 0 MM is neutral MB intermediate and BB most negatively charged and hence most mobile in an electrophoretic field[6]

Measured CK activity is similar in corresponding serum and plasma samples and not affected by therapeutic concentrations of heparin or coumadin compounds However plasma samples should be collected in EGTA rather than EDTA since magnesium required for enzymatic activity may be sequestered by EDTA Stability of CK during storage varies with the isoenzyme profile in the sample[9] MM CK collected in EGTA and mercaptoethanol is stable at room temperature for 48 hours but MB and BB are stable for only 2 hours under these conditions[10] However BB and to some extent MB are unstable at room temperature in the absence of a reducing agent which must be added promptly since loss of activity due to dissociation into subunits cannot be restored completely With refrigeration MM is stable for at least 6 days and BB and MB for 24 hours[9] With fast freezing and storage at −20° or −70 C in the presence of mercaptoethanol and EGTA MM and MB are stable for years and BB is stable for at least six months[1]

The half lives of circulating CK isoenzymes *in*

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*Creatine kinase is the preferred term rather than creatine phosphokinase since by definition kinases mediate the transfer of high energy phosphate from substrate to product

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abnormal arteries have been observed in about 50 per cent of the 65 patients whom we have studied at necropsy In the present patient, despite severe left ventricular outflow obstruction, the intramural coronary arteries were *normal* We have been unable to correlate the abnormal intramural arteries with the degree of obstruction or the presence of chest pain or any other clinical or hemodynamic parameter The abnormalities in these arteries however, are more striking than are observed in any other condition we have studied at necropsy

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Table I Creatine kinase isoenzyme distribution in human skeletal muscle

	MB isoenzyme	MM isoenzyme
Van der Veen and Willebrands 1966	±	+ + +
Dawson and Fine 196	±	+ + +
Sherwin et al 1967	±	+ + +
Trainer and Gruening 1968	–	+ + +
Magalhaes 19,0	+	+ + +
Konttinen and Somer 19 ?	–	+ + +
Roe et al 19"2	–	+ + +
Smith 19/2"	±	+ + +
Klein et al 1973	–	+ + +

Legend ± present inconsistently – absent consistently + present consistently

Table II Creatine kinase isoenzyme distribution in human tissue*

Tissue	CK (IU/Gm)	MM	MB	BB
Muscle	3?00 ± 200	3 ?00 ± 200	0	0
Heart	1 600 ± 160	1 3"0 ± 120	?30 ± 30	0
Brain	?00 ± 30	0	0	?00 ± 30
GI tract	140 ± 20	0	4 2 ± 1	136 ± 20
Adrenal	50 ± 6	0	0	50 ± 6
Lung	13 ± 2	1 ± 0.2	0	12 ± 0 5
Kidney	9 ± 2	1 ± 0 1	0	8 ± 0 5

Data obtained from references No 3, 1… 4 and unpublished observation

Results of qualitative CK isoenzyme assays

Plasma CK isoenzymes were first separated on the basis of electric charge With electrophoresis of samples at alkaline pH MM remains at the origin BB exhibits the greatest electrophoretic mobility and the mobility of MB is intermediate Supporting media for electrophoresis include agar[*] agarose[²] cellulose acetate and polyacrylamide gel [*] After separation of the isoenzymes by electrophoresis the supporting medium is incubated with reagents necessary to generate NADPH (detectable by fluorescence or dye reduction) in regions where CK isoenzyme activity is present When CK isoenzyme profiles were delineated in human tissues with these qualitative techniques brain was found to contain BB and heart MM and MB However observations with extracts from skeletal muscle were conflicting (Table I) Although in most studies only MM was detected in skeletal muscle MB was reported in some as well In view of limitations of assays based on electrophoretic techniques, stability of CK isoenzymes and recent information obtained with quantitative CK isoenzyme assays these results must be interpreted with caution In all but one of the e studies postmortem material was used Since MB is much less stable than MM it is possible that MB present initially in the tissue could have been overlooked because of tissue autolysis under these circumstances Since tissue samples were often analyzed after repetitive freezing and thawing now known to induce conformational changes in the molecule and alteration of electrophoretic mobility results may have been distorted

Nonspecific fluorescence from moieties other than CK was often not excluded by performing assays both with and without creatine phosphate the substrate specific for CK Thus, apparent MB in the skeletal muscle extract may have been an artifact unrelated to any CK isoenzyme Since electrophoretic scanning techniques are not quantitative they may have grossly overestimated the amount of MB CK activity present as was the case in early reports of MB CK content in canine myocardium representing as much as 40 per cent of total CK activity[³] and therefore twentyfold more than the 2 per cent actually present and measurable with quantitative techniques[¹] However even a small proportion of MB in skeletal muscle could be associated with release of a significant amount of MB into the circulation after intramuscular injections muscle trauma surgery or shock potentially clouding the diagnosis of myocardial infarction Thus resolution of the question of how much MB if any is present in skeletal muscle was needed

Results of quantitative CK isoenzyme assays

The kinetic fluorometric quantitative assay for CK isoenzyme developed in 1974 had a sensitivity of 2 IU/L and producibility of ± 3 per cent Human tissues removed at the time of surgery and extracted immediately prior to freezing were assayed with this technique both with and without creatine phosphate to exclude apparent activity from moieties other than CK[³] As shown in Table II myocardium was found to contain predominantly MM with MB representing approximately 15 per cent of total CK activity Skeletal muscle analyzed included deltoid pectoralis major and minor gastrocnemius and rectus abdominous all of which contained MM CK

vivo are 10 to 12 hours (MM) and 6 to 8 hours (MB) BB appears only rarely in plasma in part because of an apparently short half life [11]

Since the development of Rosalki s modification of the original Oliver assay for total CK activity [5] uniform and reproducible results have been obtained with the back reaction in which creatine phosphate is converted to ATP Reagents required are supplied from several manufacturers in kit form and provide reliable results as long as reasonable precautions are taken for quality control Activity is expressed in international units/liter with 1 IU defined as the activity required to convert 1 μmole of substrate to 1 μmole of product under reaction conditions at 30° C With assays performed at 30° (the temperature recommended by the International Union of Boochemists), the upper limit of normal for total CK is 65 IU/L and 50 IU/L for male and female subjects

Although some CK activity is present in most human tissues obtained surgically (as opposed to necropsy specimens), appreciable quantities are found in only four [3 1] Skeletal muscle is the most richly endowed source with 3200 IU/Gm Human myocardium contains 1600 IU/Gm brain 200 IU/Gm and gastrointestinal tract approximately 150 IU/Gm Other tissues such as lung (13 IU/Gm , spleen and liver (< 1 IU/Gm), and kidney (13 IU/Gm) contain almost negligible amounts No CK is detectable in human erythrocytes

Plasma CK as an index of myocardial infarction

Elevated CK activity as a criterion of myocardial infarction was first described by Dreyfus and co workers in 1960[13] and found soon after to be a sensitive index of acute myocardial injury with positive results in 95 to 100 per cent of patients [14 15] Results of studies with large numbers of patients with comparison of several enzymatic indices indicated that CK was the most sensitive [14 15]

Total plasma CK activity generally increases 4 to 8 hours after the onset of chest pain peaks within 12 to 24 hours and returns to within the normal range within 72 to 96 hours [3] However despite its sensitivity elevation of total plasma CK activity lacks specificity for the diagnosis of acute myocardial infarction with a false positive incidence of approximately 15 per cent [14] This is not surprising since total plasma CK activity increases in association with many noncardiac disorders including muscular dystrophy, inflammatory disease of muscle trauma or intramuscular injections (particularly of morphine, phenothiazines and barbiturates even without overt signs of injury) cerebral disease alcohol intoxication diabetes mellitus with and without ketosis convulsions, and psychosis—often due to CK release from skeletal muscle In addition increases in plasma CK occur with shock myxedema pulmonary embolism pneumonia radiotherapy, chronic lung disease surgery, and exercise [16 3]

High concentrations of barbiturates valium morphine, and anesthetics decrease the rate of disapparence of CK from the circulation in experimental animals and may therefore be associated with elevated plasma CK even under conditions in which release is not augmented [33] Increases have been seen as well after oral administration of aminocaproic acid, clofibrate carbenoxolone imipramine, and glutethimide [34 35]

Several cardiac conditions besides myocardial infarction may give rise to elevated total plasma CK activity Although plasma CK does not generally increase in patients with mild congestive heart failure, it may in patients with pulmonary edema and severe hepatic congestion [39] Pericarditis myocarditis electrical cardioversion and cardiac catheterization may lead to increased CK dependent upon CK release from skeletal muscle or other organs besides the heart [39 4]

Plasma CK isoenzymes and myocardial infarction

Beginning in 1966 analysis of plasma CK isoenzyme profiles was utilized to provide more specific diagnostic information regarding myocardial infarction [8] However technical limitations precluded general use of this approach until much later despite progress by Sherwin and associates [41] Trainer and colleagues [42] and others [1 43] Quantitative analysis of CK isoenzyme profiles in human tissues necessary to establish both diagnostic specificity and sensitivity of elevated plasma MB CK was hampered by lack of quantitative techniques[44] for assay of plasma CK isoenzymes until recently when a kinetic fluorometric technique was developed [7] Although laborious this method served as a useful standard for development of more convenient approaches and facilitated delineation of tissue isoenzyme profiles

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Roe et al 1972[31]	−	+ + +
Smith 1972[48]	±	+ + +
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*Data obtained from references No 3 1 47 and unpublished observations.

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exclusively. Lung, kidney, and spleen contained predominantly BB CK with no MB, and red blood cells rich in LDH and LDH_1, an isoenzyme present in myocardium, was devoid of appreciable CK activity. Although prostate and the mucosa of the small intestine contained traces of MB (< 3 per cent), myocardium was the only normal human tissue containing appreciable quantities of MB CK. Subsequent development of more rapid and convenient quantitative assays for CK isoenzymes confirmed the impression that human myocardium contains between 15 and 20 per cent MB CK and that skeletal muscle contains only MM.[51,53]

Since analysis of the CK isoenzyme profile of each skeletal muscle group is not practical, possible heterogeneity of skeletal muscle isoenzyme profiles cannot be excluded easily. Another approach has entailed analysis of *plasma* CK isoenzymes after spontaneous, surgical, or experimentally induced injury to skeletal muscle. Plasma MB CK is not elevated after intramuscular injections despite utilization of a wide variety of sites for injection and despite marked elevations of total plasma CK.[45,47] When plasma CK isoenzyme profiles were analyzed at six hour intervals for 24 hours after surgery[44] involving the head and neck, ocular muscles, thorax, abdomen, prostate, urinary bladder, or extremities, marked elevations in total plasma CK and MM CK were observed but MB CK remained normal. Analysis of CK isoenzymes by electrophoresis on agarose,[55] polyacrylaminde gel,[56] and cellulose acetate[45] demonstrated the absence of elevation of MB CK after noncardiac surgery, and serial analyses of plasma MB CK with quantitative techniques based on column and batch adsorption chromatography with Sephadex[51,5] and glycophase glass beads[51] corroborated the absence of elevated plasma MB CK after surgery.

Among 183 patients undergoing cardiac catheterization,[57] total plasma CK was often elevated, but the elevation was due exclusively to MM CK (presumably due to skeletal muscle and soft tissue trauma) in all but two cases. In the two patients with MB CK elevations, transmural myocardial infarction was the cause. In cases of rhabdomyolysis despite total CK elevations of several thousandfold, MB CK remained normal.[46] Elevated total plasma CK after exercise has been attributed to MM CK exclusively. These results of analyses of CK isoenzyme profiles in human tissues and in plasma after injury to skeletal muscle suggest that elevated plasma MB CK is a virtually specific index of injury to myocardium.[58]

Sensitivity of qualitative electrophoretic techniques for detection of MB CK is of the order of 5 to 10 IU/L.[56,7] Since plasma from normal subjects contains only 1 to 2 IU/L of MB CK, modest increases in MB CK are not recognized easily with these techniques. Nevertheless, increased activity has been detected consistently in patients with acute myocardial infarction.[1,8,11,45] In contrast, among patients with angina and only transient nonspecific electrocardiographic changes, MB CK did not increase. Operative mortality associated with coronary bypass grafting in 47 patients with unstable angina *without* elevated plasma MB CK was less than four per cent, similar though slightly greater than mortality associated with this procedure in patients with stable angina but markedly less than mortality (as high as 40 per cent) in patients undergoing surgery during evolving myocardial infarction. Thus, selection of candidates for surgery by exclusion of apparent infarction based on a lack of elevated MB CK avoids the excess mortality associated with surgery in patients with evolving infarction and suggests that absence of elevated MB reflects absence of infarction.[59] Elevated MB CK has been observed in samples from 16 of 111 patients with unstable angina characterized by recurring prolonged episodes of chest pain. However, each of these 16 patients exhibited independent evidence of acute myocardial infarction. MB CK reported in numerous studies of patients with angina without infarction as well as its absence after transitory coronary occlusion in experimental animals subjected to ischemia insufficient to produce infarction supports the view that MB CK is released from myocardium only when necrosis occurs.[1,2,3,47,57] In addition, ischemia alone induced by treadmill exercise and documented electrocardiographically in patients with coronary artery disease[60] does not lead to increased plasma MB CK despite elevated total CK, presumably from noncardiac sources.

Depletion of CK from myocardium in experimental animals correlates with morphological criteria of infarction,[41,4] the magnitude of ST segment elevation,[41] decreased blood flow measured by radioactively labelled microspheres

and alterations in frequency dependent attenuation of ultrasound indicative of infarction[64] Estimates of infarct size based on plasma CK time-activity curves correlate closely with prognosis[3] the severity of angiographically demonstrable wall motion disorders[6] and morphological estimates of infarct size in patients[7] Congestive heart failure uncomplicated by myocardial necrosis and tachycardia are not associated with elevated plasma MB CK even when total CK is increased[5, 6] Thus elevated plasma MB CK reflecting release virtually exclusively from the heart in man appears to differentiate myocardial infarction from coronary insufficiency

MB CK is particularly useful as an index of myocardial infarction occurring in patients after *noncardiac* surgery[54] Conventionally measured enzymes are elevated and LDH isoenzyme analysis may not be helpful since hemolysis leads to increases in LDH and LDH simulating the isoenzyme pattern resulting after myocardial infarction and present in myocardium itself[70] Mortality[7] associated with infarction after noncardiac surgery is high (sometimes as high as 40 per cent) possibly reflecting delay in initiating appropriate therapy because of delayed recognition of infarction Because postoperative infarction is most common in elderly patients and those with cardiac disease groups in whom definitive electrocardiographic diagnosis is often most difficult differentiation between ischemia and infarction within the first few hours after operation is difficult and may be best achieved by analysis of plasma MB CK activity[5]

On the other hand analysis of plasma MB CK activity after *cardiac* surgery does not help to establish the presence or absence of intra or perioperative infarction since MB activity is invariably elevated as a result of even minor surgical trauma to the heart[7] Furthermore since the proportion of myocardial MB CK appearing in the circulation may be much greater after surgical trauma than after infarction even quantitative evaluation of MB activity in plasma may not permit differentiation of the two Appearance of q waves on the electrocardiogram and localized positive findings on myocardial infarct scintigrams with ^{99m}Tc pyrophosphate appear to be the most useful generally available diagnostic criteria of infarction in this setting[2]

Plasma MB CK appears to remain normal in patients with pneumonia chronic lung disease and pulmonary emboli even when total plasma CK is increased[54] although elevated MB CK would be anticipated if severe right ventricular failure and ischemia led to right ventricular infarction Pericarditis has not been associated with elevated MB CK[72] but extensive associated epicarditis would be expected to liberate MB CK into the circulation

Increased total CK activity is common in patients with hypothyroidism primarily because of increased MM CK that presumably accumulates due to decreased clearance However on occasion MB CK may be elevated also It has recently been shown that hypothermia is associated with elevated plasma MM but not MB CK presumably because of enzyme release from skeletal muscle[7, 73]

Both MM and MB plasma CK are elevated consistently in patients with muscular dystrophy[76] This appears to result from failure of the normal differentiation or dedifferentiation of skeletal muscle with increasing fetal maturity and hence failure of the normal progression of isoenzyme profiles within the tissue from BB initially to MM and MB at or before term and MM alone by birth or during the neonatal interval[77] In addition MB CK in plasma in patients with muscular dystrophy may reflect release from the dystrophic heart Among patients with polymyositis elevated plasma MB CK though recognized appears to be much less consistent[74]

Available MB CK assays

Conventional clinical assays for MB CK generally employ electrophoresis of samples on agarose cellulose acetate or polyacrylamide gels—with visualization procedures capable of detecting 5 to 10 IU/L With these assays myocardial infarction can be detected with a sensitivity and specificity exceeding 95 per cent Sampling at intervals of 6 to 12 hours will usually lead to detection of even small subendocardial infarcts Exclusion of nonspecific fluorescence (and hence false positive results) with control samples run without creatine phosphate as substrate is important particularly since commonly used drugs such as tetracycline aspirin and chlorpromazine can give rise to this phenomenon (Unpublished results)

Quantitative assays offer numerous advantages including comparison of activity in all serial

samples from the same patient in view of their ability to detect some activity in plasma from normal subjects [47, 51, 5] Since development of a kinetic fluorometric technique in 1974,[47] several sensitive and more rapid quantitative procedures have been implemented Many utilize Sephadex[51, 53] or cellulose[9] to separate individual CK isoenzymes in a sample by chromatography or batch adsorption These techniques provide assays more sensitive than those based on electrophoresis and obviate the problem of nonspecific fluorescence However, incomplete separation and limited sensitivity due to dilution as well as nonspecific binding or denaturation of the enzyme on chromatographic media may pose difficulties

Recently quantitative assay of MB CK has been accomplished with a radioimmunoassay specific for the B subunit [79, 80] Lability of enzymatic activity of the antigen during the required radioactive labelling procedure and dissociation of the enzyme into subunits during incubation had precluded previous radioimmunoassay of isoenzymes of CK or other enzymes [80, 81] The methods developed to overcome these difficulties should be applicable to development of radioimmunoassays for multiple forms of other clinically important isoenzymes as well as for use in an improved quantitative assay for MB CK

The CK isoenzyme radioimmunoassay [9] detects MB CK reliably with no cross reactivity with MM despite twenty thousandfold molar excess It is more sensitive than other available assays and capable of detecting as little as 0 01 IU/L of MB CK [81] Since results are not dependent on enzyme activity but on binding of immunoreactive MB CK protein by the antibody the assay measures the concentration of enzyme protein Accordingly it should be useful in clarifying rates of turnover and denaturation of MB CK and factors influencing clearance of enzymes from the circulation after infarction Since the radioimmunoassay is so sensitive and since it can detect enzymatically inactive MB CK in the circulation it is not surprising that it permits detection of infarction earlier than other techniques usually within three hours of the onset of chest pain [8] Because radioimmunoassay is readily adaptable for automated analysis of large numbers of samples the MB CK radioimmunoassay should be generally useful for detection and assessment of severity of myocardial infarction

Some advantages of MB CK as a marker of infarction

CK is found in the heart in large quantities and confined virtually exclusively to myocardial cells as opposed to fibroblasts and other components Since the enzyme is not present in erythrocytes or leukocytes it is not released from inflammatory exudate in the heart associated with infarction After myocardial infarction, CK increases in blood within 4 to 6 hours and generally peaks within 12 to 20 hours permitting rapid diagnosis The time course of elevation of MB CK is similar but in contrast to total CK MB CK elevations are virtually specific criteria of myocardial injury The prompt diagnostic sensitivity and specificity provided by analysis of MB CK activity has important therapeutic as well as economic implications Since many patients with chest pain are admitted to coronary care units in major medical centers and community hospitals and subjected to sometimes extensive and expensive evaluations, prompt exclusion of infarction is a desirable goal When serial analyses of MB CK in plasma indicate no elevations of activity for 12 to 24 hours early transfer of the patient from the intensive care unit can be justified often permitting more efficient and economical utilization of these specialized facilities and their highly trained contingents of personnel

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Management of shock following acute myocardial infarction
Part I Drug therapy

Leslie A Kuhn M D
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About 10 years have elapsed since we evaluated the nature and treatment of cardiogenic shock in this section These years have seen some advance in elucidating the hemodynamic patterns of the shock state and in the use of a variety of therapies Regrettably however the mortality rate has remained quite high We will analyze the effects of medical therapy in Part I and the use of therapeutic mechanical circulatory assistance in Part II of these articles

Hemodynamic subsets in acute myocardial infarction

Increased use of relatively simple bedside methods to assess alterations of cardiac output by means of thermodilution techniques and left ventricular function with the aid of a Swan Ganz catheter to measure pulmonary wedge or pulmonary artery diastolic pressure (reasonably accurate gauges of left ventricular end diastolic or filling pressure) has led to more precise knowledge of hemodynamic alterations which occur following acute myocardial infarction and the effects of therapeutic interventions In addition this has permitted some correlation between hemodynamic alterations and a variety of clinical manifestations In the shock state characterized by widespread circulatory insufficiency there is almost invariably a profound reduction of cardiac index generally to below 1 8 L /min /M² Clinical degrees of hypoperfusion usually demonstrate cardiac indices of 1 8 to 2 2 L /min /M² With clinical evidence of pulmonary congestion generally the wedge pressure (or its equivalents) will exceed 18 mm Hg There are however significant exceptions to these generalizations which render precise clinical hemodynamic correlations somewhat inexact A substantial number of patients (perhaps as many as 25 per cent) without clinical suggestion of underperfusion can have appreciable reduction of cardiac index below 2 2 L / min /M² Similarly about 15 per cent of patients without clinical evidence of pulmonary congestion will demonstrate wedge pressures exceeding 18 mm Hg One common pitfall is to obtain hemodynamic measurements after urgent diuretic therapy has been administered Although rales and roentgenographic evidence of pulmonary congestion may be present there may have been rapid reduction of pulmonary wedge pressure to normal levels In chronic pulmonary disease of course râles may be present with normal cardiac output and wedge pressure In addition in some patients with chronic congestive heart failure it may be difficult to distinguish acute hemodynamic change due to the infarction from longstanding hemodynamic alterations Generally however mortality will be substantially higher in patients with wedge pressures greater than 18 mm Hg and cardiac indices below 2 2 L /min /M²

On the basis of these criteria clinical and hemodynamic subsets have been defined and correlated with mortality Thus a normal clinical and hemodynamic setting is associated with a 1 to 3 per cent mortality rate whereas clinical and hemodynamic pulmonary congestion and hypoperfusion are associated with a 51 to 60 per cent

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On the basis of these criteria clinical and hemodynamic subsets have been defined[1] and correlated with mortality Thus a *normal* clinical and hemodynamic setting is associated with a 1 to 3 per cent mortality rate whereas clinical and hemodynamic pulmonary congestion and hypoperfusion are associated with a 51 to 60 per cent

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mortality rate The shock state, characterized by hypoperfusion and profound hypotension can be considered a further subdivision of this latter group and generally has been associated with a still higher mortality rate, in most instances about 85 to 90 per cent

Vasopressors

The rationale for the use of vasopressor therapy in acute myocardial infarction with shock is based on physiological considerations as well as clinical experience Animal experiments and human studies have shown that the function of the ischemic ventricle is dependent on adequate coronary flow The principal controlling influence on coronary flow is adequate coronary perfusion pressure In a clinical setting this is generally a minimum of 80 to 90 mm Hg systolic pressure Patients in clinical shock following acute myocardial infarction will survive only rarely unless arterial pressures of at least this level are attained because continued arterial hypotension results in further deterioration of ventricular function with resultant further hypotension and circulatory insufficiency acidosis, and usually an irreversible clinical state In addition, because of continuing hypotension and its attendant myocardial ischemia, there is increased susceptibility to life threatening ventricular arrhythmias Therefore it is advisable to raise arterial pressure to about 90 to 100 mm Hg systolic as rapidly as possible A pressor agent such as norepinephrine (which also has some inotropic or beta mimetic effect) generally achieves this promptly Of course with the rise of arterial pressure from shock levels to more normal levels there is an accompanying increment in myocardial oxygen requirement but the increase in coronary flow associated with the rise of arterial pressure results in improvement of cardiac output and usually improvement of myocardial metabolism to an aerobic from an anaerobic mode as measured by alteration of lactate production [3] Therefore the net effect of norepinephrine when used in a setting with abnormally low arterial pressure in acute myocardial infarction is beneficial hemodynamically and metabolically Although mortality has remained very high in the shock syndrome with use of norepinephrine the survivors generally demonstrate an adequate arterial pressure rise Norepinephrine remains a useful agent because its effects are prompt and it is the most potent pressor available It may afford time to assess the hemodynamic and clinical situations to determine what additional modalities of treatment are necessary

Dopamine and metaraminol are also useful for the same reasons but neither is quite as prompt in its action or as potent as norepinephrine Dopamine which acts to preserve or enhance renal arterial flow in contrast to norepinephrine, is particularly useful in longstanding shock when there is substantial reduction of renal function or in patients with preexisting renal dysfunction Metaraminol can be given by the intramuscular route or by intravenous injection undiluted and does not cause sloughing of the skin if it infiltrates through the vein It has some advantage because of this in certain clinical settings where it is not feasible to prepare a diluted intravenous infusion necessary for norepinephrine administration However, it is not as potent as norepinephrine and since it is thought to depend on tissue norepinephrine for its efficacy, it may lose effectiveness during prolonged use In such instances norepinephrine may give the desired pressor effect

Inotropic agents

Inotropic agents with strong beta mimetic properties, such as isoproterenol have achieved some success when used in hypotension following cardiac surgery and in clinical states other than acute myocardial infarction In acute myocardial infarction with shock both clinical[4] and experimental[5] investigations have indicated little efficacy of this agent and some hazard Because of its inotropic effects in increasing the rate of rise of left ventricular pressure, oxygen requirement of the left ventricle is increased Since it generally fails to cause an increment in coronary perfusion pressure and flow the net effect results in persistence or increase of anaerobic ventricular metabolism and accompanying undesirable chronotropic effects However when used in a setting in which adequate arterial pressure is maintained with a pressor agent or with mechanical circulatory support beneficial hemodynamic and cardiac metabolic effects may be achieved

The use of digitalis in acute myocardial infarction has been controversial When used in normal dogs myocardial infarct size has been increased However experimental[6] and clinical[7] studies in

infarction with heart failure or shock have shown improvement towards normal of cardiac output left ventricular end diastolic pressure and myocardial metabolism The hazards due to its use are probably of minor consequence and generally controllable when the drug is used with appropriate caution Usually it is administered in somewhat lower dosage than in other situations starting with one half the digitalizing dose While favorable hemodynamic effects are achieved they rarely are sufficient by themselves to adequately reverse the shock state

A newer synthetic catecholamine dobutamine has been used in end stage congestive heart failure due to cardiomyopathy with beneficial changes in hemodynamic performance as measured echocardiographically The use of the agent in acute myocardial infarction with shock has been too sparse to form an opinion as to its efficacy at this time

Miscellaneous agents

Other agents such as high dose steroids glucose-insulin-potassium infusion and glucagon have been used with varying results particularly in experimental myocardial infarction Their efficacy and hazards in clinical acute myocardial infarction with shock have not been established sufficiently to warrant using them on other than an experimental basis at present Limitation of space does not permit full discussion of experiments concerning their use

Volume expansion

The patient with acute myocardial infarction and shock is underperfused and in those without obvious clinical congestive heart failure may often give the appearance of blood volume deficit However measurements in such patients have failed to indicate significant reductions of blood volume as a fraction of predicted normal values in comparison with patients with infarction without shock patients in the recuperative stages of myocardial infarction or in normal patients There are clinical situations in which fluid loss is obvious in the hypotensive patient such as post operative hemorrhage profound diuresis or diaphoresis or vomiting or possibly with peripheral pooling subsequent to heavy narcotic administration Generally this background is not present in the patient with acute myocardial infarction with shock and it must be determined whether fluid administration is indicated or might be harmful The most precise method of determining this is by measurement of pulmonary wedge pressure and the Swan Ganz catheter has been most valuable for this purpose If this technique is not available clinical assessment must be made and this may at times be adequate but at other times it may lead to serious error Use of right sided events such as central venous pressure measurement or clinical approximation of venous pressure by examination of the neck veins may give an erroneous view of left sided dynamics in acute myocardial infarction The function curves of the right and left ventricles differ particularly when there is predominantly left sided dysfunction as in the great majority of cases of acute myocardial infarction The right sided pressure may be normal (with normal central venous pressure) in the presence of markedly elevated left sided pressure With fluid administration in acute myocardial infarction the right sided pressure may rise only slightly but there may be great rises of left ventricular end-diastolic pressure to pulmonary edema levels[1] Therefore if the neck veins are flat and central venous pressure is *normal it should* be appreciated that fluid administration *may still* be hazardous in acute myocardial infarction If *central venous pressure* is above normal the left *sided pressure* will almost always be elevated also and generally fluid administration should be avoided One exception to this is in right ventricular infarction (which simulates inferior infarction electrocardiographically) in which instance *the right* sided pressure may be elevated and the *left sided* pressure normal Although this is *uncommon* (but perhaps more frequent than previously thought according to recent studies with radionuclide scans) fluid administration is important in restoring the depressed cardiac output and arterial pressure to normal in such patients

Traditional clinical signs of heart failure may also be misleading as pulmonary rales and dyspnea do not correlate consistently with elevated pulmonary wedge pressure Appearance of pulmonary congestion on the chest x ray may also show lack of correlation with wedge pressure because of phase lag There may be normal or even low wedge pressures when the x ray picture of congestion has not cleared and there may be elevated wedge pressures in

the absence of confirmatory chest x ray changes A third heart sound is probably the best clinical estimate of an elevated 'wedge' pressure, but this is not uniformly reliable[11]

Blood volume expansion with glucose in water, dextran or serum albumin has been reported efficacious in elevating arterial pressure and cardiac output in some patients with acute myocardial infarction and shock The number of patients responding to such treatment has varied considerably in different reports, probably owing to different definitions of shock In some, as many as 20 per cent of patients with shock are reported to be benefited by fluid administration In our own experience this therapy only very rarely relieves the shock state unless there is obvious fluid or blood loss or the patient is in the early postoperative state Some of the measurements of normal or low 'wedge' pressures have been obtained after diuretic administration In some reports and in our own experience, patients with acute myocardial infarction and shock, before treatment will almost invariably demonstrate high 'wedge' pressures generally above 15 to 18 mm Hg reflecting the profound degree of left ventricular damage known to exist in shock patients

Careful studies of ventricular function in acute myocardial infarction have demonstrated some increment of cardiac output with elevation of left ventricular filling pressure (assessed by 'wedge' pressure in most instances) to levels of about 20 to 24 mm Hg[12] Beyond this point, the function curve begins to flatten and further increments of pressure do not result in increased cardiac output, but pulmonary edema may be produced Therefore if the 'wedge' pressure is low, cautious attempts to raise the pressure to levels of about 20 mm Hg may be made However since the ability of the infarcted ventricle to eject a volume load without a sharp pressure increment may be seriously impaired because of poor compliance a relatively mild increment of volume may result in a marked rise of filling pressure and clinical signs of congestive heart failure From these considerations, it is prudent to monitor 'wedge' pressure carefully when administering volume expanding agents In our experience if hemodynamic improvement is obtained with these measures it is usually temporary unless there is an obvious fluid deficit Volume expansion is not used if the 'wedge' pressure is elevated if the patient has an S_3 or obvious clinical congestive heart failure with râles that have appeared under observation orthopnea and tachypnea

Diuretics

Diuretics, particularly rapidly acting intravenously administered furosemide or ethacrynic acid, remain the most important agents for symptomatic relief of congestive heart failure and for prompt, predictable lowering of elevated left ventricular diastolic pressure whether or not shock is present They usually produce little rise of cardiac output, but a small reduction of ventricular volume can result in a substantial fall of ventricular diastolic pressure Despite small alteration of cardiac output the patient generally improves substantially symptomatically and there may be prompt relief of tachypnea and orthopnea with their attendant apprehension and tachycardia It is probable that susceptibility to life threatening arrhythmias is diminished by reduction of elevated ventricular volume and ventricular diastolic pressure Therefore the prompt administration of these agents when congestive heart failure is present is important and is usually beneficial

Vasodilators

There has been a rapidly growing literature concerning the use of a variety of 'vasodilators' in congestive heart failure with and without acute myocardial infarction In general, cardiac output has risen moderately and elevated 'wedge' pressure has shown a somewhat more marked decline Different drugs classified as 'vasodilators' may have differing actions Nitroglycerin and the long acting nitrates act primarily to reduce preload hydralazine to reduce impedance and afterload and nitroprusside has dual effects There is some evidence that nitroglycerin and nitroprusside may have different effects on the coronary circulation nitroglycerin enhancing flow to ischemic areas and nitroprusside failing to do this producing increased ischemia[13] When the 'wedge' pressure is normal or reduced vasodilators may cause a further fall of an already depressed cardiac output[14] In addition nitroprusside infusion has been associated with a reduction of arterial oxygen pressure probably due to increased perfusion of underventilated portions of the lungs[15]

Despite the favorable hemodynamic altera

tions produced by these agents in congestive heart failure their precise role in the treatment of acute myocardial infarction has not been fully delineated They are most rational when the arterial pressure is substantially elevated and there is recurrent ischemic pain and congestive heart failure particularly in association with significant mitral regurgitation where reduction of peripheral vascular resistance causes reduction of the regurgitant fraction and enhanced forward flow In normotensive patients with congestive heart failure while there may be measurable hemodynamic improvement with the vasodilators the patient may usually be managed with conventional diuretics and digitalis In severe heart failure the vasodilators may be useful but rarely are sufficiently efficacious by themselves

In the patient with acute myocardial infarction with shock there have been some reports of successful use of vasodilators with reduction of early mortality to about 50 per cent (with disappointing results for post hospitalization salvage) [9] However favorable results in shock have not been attained consistently and there are considerable hazards to their use This difference in reported survival with the use of these and other agents in cardiogenic shock probably results from different definitions of the shock syndrome When marked arterial pressure reduction to below 80 to 90 mm Hg systolic is an integral part of the definition results of therapeutic interventions are almost uniformly more pessimistic than when the syndrome is more loosely defined by reduction of cardiac output or reduction of arterial pressure to a percentage of what it was in the preinfarction state In such instances the natural course of the disease and its treatment with conventional agents are more favorable as there is probably less profound myocardial damage There are no adequate randomized studies in different groups of patients using the therapeutic agents advocated for the treatment of shock following acute myocardial infarction

A priori it would appear undesirable to use an agent which can further depress an already critically low arterial pressure While the vasodilators can often achieve reduction of ventricular diastolic pressure and elevation of cardiac output without a significant fall of arterial pressure their actions at other times are unpredictable and substantial falls of arterial pressure may result from relatively small doses Generally at low doses this will not occur and reduction of cardiac output and arterial pressure are more commonly seen at medium to high dose levels but we have observed several instances of profound arterial pressure reduction with low doses of nitroprusside or nitrates Hemodynamic monitoring of wedge and arterial pressures is of prime importance when these agents are used particularly when the patient is hypotensive and care must be taken not to allow significant reduction of the already depressed arterial pressure The impact of vasodilators in the shock state is probably minor in regard to patient survival but it is probable they may be useful adjuvants when used with other modalities which can maintain arterial pressure such as the intra aortic balloon or pressor agents

Conclusions

Shock following acute myocardial infarction when defined reasonably rigidly to include arterial systolic hypotension of below 80 to 90 mm Hg in association with signs of underperfusion continues to cause very high mortality despite all attempts at therapy Vasopressor agents are generally effective in promptly restoring arterial pressure towards normal Subsequent treatment relies on clinical observations and hemodynamic measurements Diuretics are helpful in promptly reverting pulmonary congestion Digitalis may be used as an adjuvant agent Other inotropic drugs such as isoproterenol generally are ineffective and may be hazardous when used in a hypotensive patient with acute myocardial infarction Blood volume expansion is helpful in the patient with reduction of cardiac output and low ventricular filling pressure an unusual circumstance in shock following myocardial infarction unless there has been obvious fluid loss The benefits of vasodilator agents have not been fully established in the shock state and they may be hazardous sometimes unpredictably causing further depression of an already low arterial pressure

Although drug therapy can be more intelligently managed with the aid of appropriate hemodynamic measurements and there are some survivors attributable to pharmacologic agents the great majority of patients are not ultimately successfully treated This is because there is profound myocardial damage once shock has developed and in many instances it is irreversible

For significant improvement in mortality rate attention must be directed toward prevention of the shock state by vigorous management of lesser degrees of heart failure, early hypoperfusion and significant arrhythmias, all of which may culminate in shock

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Annotations

Of teaching hygiene

Several decades ago hygiene was a mandatory part of the elementary and high school curricula for all children of America Children were taught *to wash their hands* as well as why how and when to do so They were taught the proper care of teeth and oral hygiene They learned to use soap and water and the need for bathing regularly They learned about diseases and infections contagious illnesses and nutritional illnesses They learned about germs bacterial and viral and they learned where these agents resided in great abundance *how they infected man their portal of entry the diseases they* produced and the methods of their dissemination Children *were taught* the fundamentals of nutrition play rest sleep happiness obedience and discipline They learned of the respective roles of their parents teachers and fellow students The importance of early care of illnesses the need of adequate lighting to read and study and the value of fresh clean air were all *discussed in the classroom* The students learned about toxic agents and how to avoid them Their hands and fingernails were inspected daily by the teachers The children were advised to keep their hands clean *their nails trimmed* and their clothes clean and neat regardless of the cost or quality of the clothing Students learned to be proud and loyal to America, how to play together win or lose These and many other important instructions for mental and physical health and for happiness were taught regularly each year Good physical and mental health and happiness of the students were the concerns of the teachers Students learned the proper sense of values for good mental health as well as for good *physical health.*

But today there is *little or no hygiene* taught Habit forming drugs are known to be used in high schools and *even* in elementary schools at present Permissiveness and sexual behavior are the concerns of today

One merely has to observe people entering and leaving public *restrooms to see how inadequately* they wash their hands if they wash them at all People cough and sneeze into the faces of others and *blow their nasty tobacco smoke into* the faces of those about them

Few children have seen a bacterium protozoan or virus under a microscope or have learned anything concerning their characteristic features

Why are there no more classes in hygiene? Why *not teach* the hazards of insecticidal sprays Lysol spray deodorant sprays hair sprays, and other agents and practices *that are so* toxic and that are polluting the American home? It is well known that preventive medicine is more important than curative medicine There is no doubt about that So shouldn t hygiene be a part of all elementary and high school curricula and be taught by knowledgeable teachers?

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The problem of cell aggregation during coronary artery bypass procedures

The mechanical transfer of blood during cardiac bypass procedures *has often been complicated by the problem of* particle aggregate formation and the need to *remove these* aggregates through filtering It is common practice to attempt to control this difficulty *through* the use of heparin the rationale being that the anticoagulant *properties* of heparin will serve to disperse particles and keep *aggregation* from occuring Experience to date however *indicates* that heparin even in high concentrations often fails to prevent *or reverse* the process of aggregation

To the best of our knowledge *no satisfactory* proposal presently exists to account for particle *formation* under these conditions in the lines of the pump and *presumably* in the blood stream of the patient nor has a *rationale of prophylaxis* been available to prevent this potentially adverse development

In our laboratory in vitro experiments have demonstrated that *when a drug such as* heparin is added in increasing doses to whole blood a *concentration*-dependent biphasic reaction results Both microscopic *and sedimentation rate studies* indicated that with *low concentrations* of heparin dispersion of red blood cells occur This phenomena constitutes the first phase *However* with addition of increasing concentrations of heparin these cells were observed to aggregate Replication of this experiment *using a different* molecule for each experiment i.e. coumadin albumin mucopolysaccarides etc yielded the same biphasic *pattern of dispersal followed* by aggregation

It is our proposal that the observed reaction of dispersal followed by aggregation is a function of the surface active properties of the heparin coumadin etc molecules acting on the surfaces of cells and the surfaces of other particles present in the blood Heparin or other surfactant molecules accummulating at the cell surfaces form films adjacent films then adhere to each other causing aggregation to occur Albumin and fragments of cells are also capable of layering out on surfaces to form films and in a manner similar to that exerted by high concentrations of heparin to produce aggregation The point to be emphasized is that to prevent particle aggregation an *optimal* concentration of the anticoagulating or antiaggregating agent must be present in the circulating blood during the bypass procedures *Optimal* is used to mean that concentration of drug at which dispersion has fully occurred and beyond which aggregation will be initiated This concentration can be quickly and empirically determined through microscopic examination of blood samples which are routinely drawn during bypass surgery

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To each according to his desert

Bed rest is one measure which is generally used in the management of a patient with acute myocardial infarction The length of bed rest of such patients varied a great deal with the passage of time According to Lewis rest in bed should be continued for at least eight weeks even in the milder cases to ensure firm cicatrisation of the ventricular wall A number of patients have lost their lives and especially those who have early recovered from symptoms by neglect of these precautions Most authors recommended a bed rest of six weeks duration This is a far cry from the few days of bed rest advocated lately The long bed rest in general use was influenced by a few experimental studies performed by pathologists

As early as 1916 Karsner and Dwyer[2] had found necrotic tissue in the myocardium 60 days after ligation of a coronary artery in dogs More than two decades later Mallory White and Salcedo Salzar[3] in their classical paper showed that it took five weeks for the removal of necrotic material after an infarction While small infarctions in dogs healed in about five weeks large ones healed completely in two months Therefore to every clinician the long bed rest for patients with acute myocardial infarction seemed to be absolutely necessary This viewpoint found support in a study which revealed a higher incidence of rupture of the myocardium in mental patients with acute myocardial infarction who were ambulatory 73 per cent of patients with an acute myocardial infarction died from cardiac rupture and tamponade Furthermore experiments on dogs showed that after ligation of the ramus descendens anterior rest led to healing of the infarction with production of a small firm scar without thinning of the ventricular wall while early exercise (within three days after the operation) resulted in thin scars with aneurysmal bulging

The often quoted experiments by Thomas and Harrison are not pertinent because the myocardium was only slightly damaged by burning the authors themselves caution not to draw conclusions concerning patients

For many years now perhaps influenced by statements pointing out the harm done by prolonged bed rest patients with acute myocardial infarction were asked to be out of bed early and were discharged early from the hospital Already in 1959 Brummer and colleagues questioned the need for long bed rest in the management of acute myocardial infarction Groden and associates[10] did not find any significant difference in mortality rate development of hypotension shock or heart failure further episodes of chest pain incidence of arrhythmias in two groups of patients with acute myocardial infarction when mobilized early or late and discharged from the hospital early or late The authors also state that there was no difference in the long term incidence of ventricular aneurysms in the two groups One of their groups stayed in the hospital three weeks and the other five weeks

In addition to venous thrombosis and pulmonary embolism muscular atrophy economic and psychologic effects were mentioned as arguments against prolonged bed rest thus completely disregarding the findings of pathologists mentioned above It is also significant with today s reliance on instrumental findings that in more recent studies the presence or absence of gallop rhythm distant muffled heart sounds râles over the bases of the lungs often even the level of blood pressure are not considered in a decision of the duration of bed rest

In numerous recent studies more authors tried to demonstrate that still earlier ambulation and earlier discharge from the hospital did not increase mortality and morbidity and did not lead to the formation of a cardiac aneurysm Some authors discharge patients with acute myocardial infarction even after 7 or 10 days if no complications have been observed and some went even so far as to find bed rest unnecessary Shah while concluding that physical activity after myocardial infarction was associated with reduced mortality noted that there was also association with increasing effort intolerance between 18 months and two years after the acute attack This delayed disability of those patients who did not follow the conventional bed rest was not explained by the author Abraham and co workers in a prospective randomized study came to the unusual conclusion that early mobilization is beneficial irrespective of

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complications on admission in patients with acute myocardial infarction Hurst on the other hand in an Editorial in the same issue scrutinizes the article by Abraham and colleagues and finds certain deficiencies in the type of investigation these authors followed in their study and concludes that common sense dictates that patient management should be individualized and that this matter is under active study by many people Mather and associates even considered home care preferable for many patients particularly older ones and—strangely enough—for those with initial hypotension Wingo and Lopez found early ambulation even beneficial in patients admitted with complications Collins maintains that the decision whether hospital or home care is desirable depends on the status of the patient two hours after the start of symptoms. Some other investigators arrive also at remarkable conclusions Wilson and Pantridge base the early discharge from the hospital of their patients on the degree of the RS-T segment displacement Earlier studies however have demonstrated in experiments on dogs that very small and superficial lesions of the heart for instance brushing a 10 per cent solution of sodium chloride on an area as large as one square centimenter or mechanical le ion of such an area may cause a marked displacement of the RS T segment Chaturvedi and colleagues discharged from the hospital 68 per cent of their patients with acute myocardial infarction by the seventh day However persistence of RS T elevation of more than two millimeters six days after the onset of the infarction argues against an early discharge

In an Editorial it is stated that in a majority of uncomplicated infarctions, immobilization for more than seven days is not justified Hayes and co workers removed from the coronary care unit after 48 hours patients when they were free of pain heart failure and arrhythmias These patients were discharged from the hospital nine days after the onset of the infarction. However such patients not rarely develop later transmural infarctions

Despite the numerous studies mentioned above we are convinced that early mobilization and discharge from the hospital of patients with acute myocardial infarction is associated with more frequent complications particularly congestive heart failure and ventricular aneurysm It is established that the amount of circulating blood increases when patients change from complete bed rest to even slight physical activity due to sudden mobilization of blood from the depots this increased circulating blood volume returns to the heart and bulging of the damaged portion of the myocardium is understandable This would not occur in small subendocardial infarctions but in transmural infarctions readily recognized in the electrocardiogram the situation is different The point must be stressed that the clinical diagnosis of cardiac aneurysms even with the aid of the X ray studies is very difficult and often missed (unless one uses invasive procedure) In addition sudden dilatation of the heart may lead to congestive heart failure

Because of the many papers of recent vintage recommending a short stay in the hospital of patients with acute myocardial infarction Utilization and Peer Review Committees insist on quick dis harge of su h patients The decision is often made within the first hours after admission of the patient without regard to later developments

Repeatedly we observed patients with acute myocardial infarction who after discharge from the hospital developed gallop rhythm distant impure heart sounds and pulmonary congestion These patients improved markedly when in addition to medication rest (nor absolute bed rest) was recommended for several weeks or even months Some of these patients remained symptom free for years afterward

It must be stressed that not every clinician finds an early mobilization of patients with acute myocardial infarction justifiable Thus Blumgart and Zoll sound a warning directed toward the advocates of early mobilization and "emphasize the importance of rest and reduced activity for many weeks after acute myocardial infarction Weingarten and colleagues observed 35 patients with acute myocardial infarction for 4 to 14 months after early discharge from the hospital. All had been mobilized by the sixth day and were discharged after up to 15 days after hospitalization Two of these patients were readmitted because of a new infarction two developed congestive heart failure and one of these died In another study the recurrence of myocardial infarction within months after dismissal from the hospital of patients who were ambulated early was very high In a recent Editorial Miller* takes a compromise attitude when he assumes that around three weeks of hospitalization offers a reasonable middle route to follow" and emphasizes that It remains to be established whether there is any value to early mobilization other than the psychological benefit "

Generalizations on this subject are not justified Sensible individualization is necessary and every patient has to be evaluated according to the clinical findings

Our tentative suggestions are as follows For small "intramural" or subendocardial infarctions, without complications we recommend one week of bed rest and discharge from the hospital after 14 to ?0 days. In larger and especially transmural infarctions, without complications, we advise bed rest of three to four weeks and discharge in four to five weeks. Any significant complication will cause lengthening of the time of bed rest and hospital stay it is well recognized that complications may arise suddenly and unexpectedly even in the mildest case namely in patients with a "small" infarction

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Table 1 Expected mortality for cohort

Age (years)	n	Mortality p	np	Risk factors		Adjusted mortality	
				f	f	np/f	np/f
< 29	5 540	1 8	0 10	8 4	5 00	01	02
30-39	2,393	20 5	0 49	7.3	4.50	07	11
40-49	1 439	122 0	1 71	6 27	4 00	27	43
50-59	463	403 0	1.85	4 96	3 21	37	58
60-64	79	841 0	0 66	4 36	1 74	15	38
64 69	32	1 234 0	0 39	3 76	1 87	10	21
> 70	12	1 704 0	0 17	3 16	1 99	05	16
Total	9 958	186 0†	5 37	5 19	2 86	1 0[illegible]	1 89

†Average for all ages.

the expected mortality rate per year for this group Columns 5 and 6 indicate the smoking weight combined risk factors computed with slightly different assumptions for each column The two final columns present the annual mortality rate expected for the 9 958 men who do not smoke and are less than 90 per cent of average adjusted weights We see that we may anticipate one or two deaths per annum from ischemic and related heart disease

It is clear that statistics which under alternative initial conditions (marathoners vs a non smoking thin non running age adjusted control group) achieve only a difference of 1 or 2 deaths per year (and this difference requires the assumption that marathoning confers absolute protection) are statistics that are not able to assess meaningful differences in the risk factors appropriate to the two groups I must conclude that only a formal long term prospective epidemiological study that utilizes an appropriate control group can be expected to provide a data base from which valid conclusions can be extracted.

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Statistics, marathoning and CHD

Many reports have appeared in the last decade that describe epidemiological studies of the relationship between physical activity and mortality especially mortality from coronary heart disease The methodological and epidemiological problems encountered by these studies are extreme and valid conclusions are notoriously difficult to achieve Yet Bassler has written that a search of the literature failed to document a single death due to coronary arteriosclerosis among marathon finishers and in a subsequent letter he concludes that when the level of vigorous exercise is raised high enough the protection appears to be absolute The American Medical Joggers Association has been unable to document a single death resulting from coronary heart disease among marathon finishers of any age We do not know what significance we are to place upon Bassler s communications we do not know how many deaths of marathoners—from all causes—was revealed by the search of the literature conducted by Bassler nor do we know the number of autopsies performed or reviewed by the A M J A both crucial facts for establishing the statistical significance of his findings

I have made some calculations which bear on this In 1975 10 482 men and women completed a marathon road race Approximately 5 per cent of these runners were women leaving 9 958 male marathoners I have estimated the number of men expected to die from ischemic and related heart disease in a cohort of 9 958 white American males whose age distribution is the same as these marathoners but whose relative weight level of exercise and smoking habits are the same as the general American insured male population However marathoners almost to a man (or to a woman) are invariably quite thin and not addicted to smoking After applying appropriate weight and smoking risk factor corrections to the estimated mortality rate for these men we may obtain an estimate of the number of men that would be expected to die per year in this non running non smoking non average weighted group of men This estimate then is independent of any postulated protection that marathoning might afford Table I columns 1 and 2 show the age distribution of the marathoners column 3 the annual mortality rate per 10 for each age interval for white insured U S males and column 4

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Fig 1 Mutilation of SA nodes which occurred during autopsy thereby impairing the study of two interesting cases—one from Italy and one from Portugal. (Hematoxylin and eosin ×10)

Thorough histologic study of the pacemaker is always hampered by these injuries and sometimes impeded

Surely it is nonsensical to sacrifice the very heart a heart on the autopsy table to mere manual habit

One can avoid any damage to the SA node by simply extending the lateral incision of right ventricle and AV ring posteriorly into the ostium of the inferior vena cava instead of the superior Through this wide gap the inner atrial wall can be inspected it can be turned inside out the intercaval bridge can be further cut lengthwise as medially as possible

Suggestions have been put forward on the matter without apparent success a strong authoritative and far reaching plea to salvage the pacemaker at autopsy is needed in order to secure basic morphologic knowledge in the field of arrhythmias.

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Reactions to furosemide

To the Editor

In the July 1977 issue of THIS JOURNAL (94 6 1977) Dr Greenblatt and colleagues conclude that furosemide is a relatively safe diuretic in a wide range of clinical situations, based on the observation of a 10 1 per cent incidence of adverse reactions among 2 367 hospitalized patients in whom only two deaths were felt to be *furosemide related* They found the data reassuring since serious toxicity was unusual

While not necessarily disagreeing with their conclusions, we would like to point out that the authors criteria for serious toxicity are not mentioned in the *article* In addition it is not clear how aggressively possible reactions were sought Were audiograms routinely *performed* before and after furosemide therapy or was the patient required to complain of hearing difficulties? There is abundant literature implicating furosemide as a potentially ototoxic drug Were the drugs whose toxicities are known to be potentiated by furosemide such as cephaloridine lithium aminoglycoside antibiotics and curariform drugs included in the tabulation?

There were 390 patients in the report who carried a diagnosis of "congestive heart failure and 164 patients acute myocardial infarction " As is pointed out in a recent article edited by one of the investigators, patients with chronic congestive heart failure have been noted to have decreased blood pressure and cardiac output with elevated systemic vascular resistance "diuretics may be effective but are very likely to decrease cardiac output further and to impair renal function still more In acute myocardial infarction sudden massive diuresis in patients with normal filling pressures might be expected to reduce cardiac output and adversely affect the myocardial oxygen supply/demand balance We wonder how carefully hemodynamic parameters were monitored in the reported patients. Volume depletion was cited as the commonest adverse reaction based on the finding of elevated blood urea nitrogen in many cases. Were indices of creatinine clearance monitored too? Patients with many of the illnesses represented have in our experience diminished appetite and protein intake Consequently blood urea nitrogen might not be a sensitive *measure of volume* status or nephrotoxicity

In summary we do not disagree *with Dr Greenblatt* and associates enthusiasm for furosemide as a safe diuretic " However we do *not feel that their* article has proved the conclusions stated It should be recalled that 16.3 per cent of their patients died during *hospitalization Moreover* how many receiving furosemide as outpatients suffered consequences in the unsupervised milieu of home is not clear We believe that the potent loop diuretics should still be respected and that appropriate monitoring for *adverse effects* should accompany their use

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The opinions and assertions contained herein are those of the authors and are not to be *construed as* official or necessarily reflecting the view of the Medical Department of the Navy or the Naval Service at large

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Letters to the Editor

Needed An F D A for surgery?

To the Editor

If heart attacks were caused by germs it properly would be said that we the people are in the midst of a raging epidemic of a highly lethal disease If the medical profession advised for the treatment of this epidemic the widespread use of an incredibly expensive painful treatment having a small but definite mortality rate of its own and yet a treatment which had not yet been proved to prolong life in the great majority of cases it properly could (and would) be said of us that we are a bunch of fools This precisely is the state of affairs today for coronary bypass surgery If a wise and dispassionate onlooker were to say that there must be a better way he would be right There is

Much public agitation occurred recently when the popular press reported the results of a scientific study which purported to demonstrate that coronary bypass surgery does not prolong life While the validity of this conclusion is open to some question what is not open to question is that this kind of proof is being sought years too late

Insofar as drugs are concerned the medical community long has taken the position and rightly so that the burden of proof is on the protagonist who claims safety and efficacy for a new drug Right from the beginning it is up to the drug manufacturer to prove that his drug works and that the risk of taking the drug is less than the risk of having the untreated disease Until he does so the drug is prohibited by the F D A from being sold on the open market Undoubtedly some lives may be lost by such a cautious approach but the attitude of our profession is when in doubt an error of omission is better than an error of commission Above all do no harm is a venerable and deeply held medical axiom

Unfortunately this policy rarely if ever is followed for surgical procedures A new operation no matter how bizarre often can be championed by a surgeon without any proof whatsoever other than his intuitive (and often erroneous) experience if the hospital medical staff and administration are compliant As first tens then hundred and finally thousands upon thousands of these operations are done bits and pieces of positive and negative information are accumulated but more often than not even then a firm scientific foundation for the operation still cannot be given

This is the present sad state of affairs for coronary bypass surgery Ten years down the line and after tens of thousands of operations have been performed only recently are we asking for the kind of rigid scientific proof that should have been demanded right from the start If (as seems probable) a suitable animal model could not have been fashioned then the procedure should have been labeled an experimental procedure and handled in the same way as a new and unproved drug would have been handled The initial trials should have been limited to a few authorized hospitals which were prepared to conduct these trials under strict scientific conditions conditions calculated to yield the maximum amount of information with the least risk to the patients

Let this experience be a lesson to us Henceforth we should require of new surgical procedures what we now require of new drugs Our bull dog posture should be Show me!

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Fructose and triglycerides

To the Editor

In an Annotation in your JOURNAL of December 1974 Roberts calls attention to the relation between dietary sucrose and triglyceride levels It is interesting to note that papers published by other authors show that this action is due to fructose[1, 2] Our previous work showed that it is possible to know the reaction of the patients by means of a load of 100 gm of fructose[3] With this procedure it is possible to know if the patients need a restriction of sucrose in the diet

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Salvage the pacemaker at autopsy

To the Editor

Frequently I receive autopsy material from various sources both Italy and abroad for clinicopathologic control of the conducting system It is most distressing to note how often serious injury has been inflicted on the cardiac specific tissue by the customary postmortem procedures in the hands of pathologists who have not been warned or who do not specialize in cardiac tissue All too often the sinoatrial (SA) node (Fig 1) has been badly slashed by the traditional handbook incision driven alongside the right atrioventricular (AV) walls and positioned laterally in the superior vena cava Often there is a lengthwise cut in the intercaval bridge as well

Recent Advances in Vascular D seases Edited by Arnold Kappert Hans Jorg Leu and Peter Waibel Bern Stuttgart Vienna 19 6 Hans Huber Publishers 159 pages Price $9 7o

This paperback book contains all the papers publi_hed in Engush during 19 5 in VASA a journal devoted to vascular diseases The papers are grouped according to subjects namely microcirculation research angiography and clinical practice This book should interest all physicians and surgeons who treat peripheral vascular disease since the various papers are diversified and would interest anyone There is a need to learn more about peripheral vascular diseases and to realize more fully that the principles of peripheral vascular physi ology and peripheral vascular disease states apply to the vascular system of all organs not only to that of the limbs Peripheral vascular diseases are common and need more serious consideration in training programs in medicine espe cially cardiovascular training programs VASA is a journal that needs more attention by practicing physicians The editors of this book have provided a fine service to physicians and trainees as well as to the journal VASA

Mechanical Support of the Fa l ng Heart and Lungs Edited by David Bregman New York, 19 7 Appleton Century Crofts 210 pages

Bregman and the 28 contributing authors have produced a book of seven chapters with appended discussions on a special and highly technical procedure The use of circulatory support is in its developmental stages at present Those in the field both clinical and research will find this book of considerable value to them while those in cardiology will need this book as a source of information concerning the thinking of the contrib utors The discussions are interesting and reveal the limita tions in the present state of knowledge and technics This book is concerned with a highly specialized procedure which is of more than cursory interest to only a few cardiovascular surgeons and cardiologists

Pathophys ologie Diagnost k Therapy—Herzkrankhe ten Edited by H Reindell and H Roskamm Berlin 1977 Sprin ger Verlag 9 0 pages. Price $ 6 60

Reindell and Roskamm have edited a textbook on heart disease with emphasis on pathophysiology diagnosis and treatment and which integrates these three a_pects of clinical cardiology extremely well The approach is different from most textbooks on heart disease in that the mechanism of disease is constantly related to the clinical syndromes discussed throughout the book The brief descriptions of anatomic and physiologic peculiarities of the cardiac pump are well supported by well selected illustrations Chapters on the more sophisticated diagnostic technics are good and include phonocardiography arterial and venous blood pressure recording vectorcardiography echocardiography coronary angiography and impedance plethysmography among others Even though the book contains almost one thousand pages the two editors and other contributors present only selected aspects of cardiology

Since this book emphasizes pathophysiology pathology and hemodynamic phenomena so well it should serve as an excellent supplement to the existing books which are less concerned with these important a_pects of cardiology The book should be translated into English in order to reach a larger audience Furthermore physiologists and pathologists who teach medical students will find the book to be useful in planning their course presentations in cardiology and hemo dynamic physiology The book is highly recommended to medical students as well as to those training in and practicing cardiology It must be added that the publishers have done an excellent job in the production of this book

Case Studies in Echocardiography A D agnostic Workbook By Ralph D Clark M D Philadelphia 1977 W B Saunders Company 334 pages Price $14 95

Clark s case study book on echocardiography is a very good publication on the subject The cases are well selected and the discussions are good The illustrations are a little blurry but adequate for study Readers will find this book to provide them not only with an opportunity to learn ECHO but to compare their interpretations and recording technic with Clark s. The discussions are good, but without the entire strip of recording the sections selected do handicap interpretations This is well illustrated by Case 37 Nevertheless readers who patiently study each ca_e will profit immeasurably by this book The section on measurements and calculations is useful for beginners as well as for experienced echocardiographers This is a valuable addition to this rapidly expanding diag nostic procedure in cardiology

Reply

To the Editor

Our paper on adverse reactions to furosemide cited several references[1-3] that describe in detail the methodology of the Boston Collaborative Drug Surveillance Program (BCDSP) The monitoring system used by the BCDSP is integrated into the routine operation of the medical ward and does not interfere with that routine All decisions regarding diagnostic tests and therapeutic measures are made by house staff or attending physicians responsible for the care of these patients and are based solely upon clinical needs The recording of an adverse drug reaction defined as an unintended or undesired drug *effect is also based upon the clinical judgment of* treating physicians later corroborated by a clinical pharmacologist who reviews the case In most instances these adverse drug reactions are of sufficient clinical importance to necessitate drug discontinuation alteration of dosage or institution of some specific therapeutic measure We realize that certain limitations and uncertainties are inherent in this approach to comprehensive drug surveillance However the 11 year experience of the BCDSP which now involves more than 35 000 hospitalized medical patients indicates that the data provide a reasonably accurate description of clinical drug effects in this setting

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1 Miller R R and Greenblatt D J Editors Drug Effects in Hospitalized Patients Experiences of the Boston Collaborative Drug Surveillance Program 1966-1975 New York 1976 John Wiley & Sons
2. Allen M D and Greenblatt D J Role of nurse and pharmacist monitors in the Boston Collaborative Drug Surveillance Program Drug Intell Clin Pharmacol 9 648 1975
3 Jick H Drugs—remarkably nontoxic N Engl J Med 291 824 1974

Recent Advances in Vascular Diseases Edited by Arnold Kappert, Hans Jorg Leu and Peter Waibel. Bern, Stuttgart, Vienna, 1976, Hans Huber Publishers, 159 pages. Price $9.75.

This paperback book contains all the papers published in English during 1975 in *VASA*, a journal devoted to vascular diseases. The papers are grouped according to subjects, namely microcirculation research, angiography, and clinical practice. This book should interest all physicians and surgeons who treat peripheral vascular disease, since the various papers are diversified and would interest anyone. There is a need to learn more about peripheral vascular diseases and to realize more fully that the principles of peripheral vascular physiology and peripheral vascular disease states apply to the vascular system of all organs, not only to that of the limbs. Peripheral vascular diseases are common and need more serious consideration in training programs in medicine, especially cardiovascular training programs. *VASA* is a journal that needs more attention by practicing physicians. The editors of this book have provided a fine service to physicians and trainees as well as to the journal *VASA*.

Mechanical Support of the Failing Heart and Lungs Edited by David Bregman. New York, 1977, Appleton-Century-Crofts, 210 pages.

Bregman and the 28 contributing authors have produced a book of seven chapters with appended discussions on a special and highly technical procedure. The use of circulatory support is in its developmental stages at present. Those in the field, both clinical and research, will find this book of considerable value to them, while those in cardiology will need this book as a source of information concerning the thinking of the contributors. The discussions are interesting and reveal the limitations in the present state of knowledge and technics. This book is concerned with a highly specialized procedure which is of more than cursory interest to only a few cardiovascular surgeons and cardiologists.

Pathophysiologie, Diagnostik, Therapy—Herzkrankheiten Edited by H. Reindell and H. Roskamm. Berlin, 1977, Springer Verlag, 930 pages. Price $56.60.

Reindell and Roskamm have edited a textbook on heart disease with emphasis on pathophysiology, diagnosis, and treatment and which integrates these three aspects of clinical cardiology extremely well. The approach is different from most textbooks on heart disease in that the mechanism of disease is constantly related to the clinical syndromes discussed throughout the book. The brief descriptions of anatomic and physiologic peculiarities of the cardiac pump are well supported by well-selected illustrations. Chapters on the more sophisticated diagnostic technics are good and include phonocardiography, arterial and venous blood pressure recording, vectorcardiography, echocardiography, coronary angiography, and impedance plethysmography, among others. Even though the book contains almost one thousand pages, the two editors and other contributors present only selected aspects of cardiology.

Since this book emphasizes pathophysiology, pathology, and hemodynamic phenomena so well, it should serve as an excellent supplement to the existing books which are less concerned with these important aspects of cardiology. The book should be translated into English in order to reach a larger audience. Furthermore, physiologists and pathologists who teach medical students will find the book to be useful in planning their course presentations in cardiology and hemodynamic physiology. The book is highly recommended to medical students as well as to those training in and practicing cardiology. It must be added that the publishers have done an excellent job in the production of this book.

Case Studies in Echocardiography. A Diagnostic Workbook By Ralph D. Clark, M.D. Philadelphia, 1977, W. B. Saunders Company, 334 pages. Price $14.95.

Clark's case study book on echocardiography is a very good publication on the subject. The cases are well selected and the discussions are good. The illustrations are a little blurry but adequate for study. Readers will find this book to provide them not only with an opportunity to learn ECHO but to compare their interpretations and recording technic with Clark's. The discussions are good, but without the entire strip of recording the sections selected do handicap interpretations. This is well illustrated by *Case 37*. Nevertheless, readers who patiently study each case will profit immeasurably by this book. The section on measurements and calculations is useful for beginners as well as for experienced echocardiographers. This is a valuable addition to this rapidly expanding diagnostic procedure in cardiology.

Books received

Physiology for the Anesthesiologist By Nishan G Goudsouzian and Agop Karamanian New York 1977 Appleton Century Crofts 388 pages Price $22 50

Pulmonary Pathophysiology the Essentials By John B West M D Ph D Baltimore 1977 The Williams & Wilkins Company 198 pages Price $9 95

Infectious Diseases 2nd edition Edited by Paul D Hoeprich M D Hagerstown Md 1977 Harper & Row Publishers Inc 1258 pages Price $42 50

Respiratory Disease Edited by D J Lane New York 1977 Appleton Century Crofts 553 pages Price $28 50

High Risk Pregnancy and Child By Z Stembera K Znamenacek and K Polacek Littleton Mass 1977 PSG Publishing Co Inc 307 pages Price $25 00

The Hemoglobinopathies Techniques of Identification By Titus H J Huisman and J H P Jonxis New York 1977 Marcel Dekker Inc 464 pages Price $44 00

Announcements

Health Sciences Communications Association meeting

The twentieth annual Health Sciences Communication Association meeting will be held in May 1978 in Tucson Arizona The program title is HeSCA del Sol The Communications Spectrum HeSCA communications activities will be viewed in their relation to Among Professional Specialties Beyond Institutional Walls Across the Community and Culture and Over National Boundaries For further information regarding this meeting contact Beverly Hill Chairperson Promotions Committee Director of Biocommunications School of Pharmacy 1985 Zonal Ave Los Angeles Calif 90033

American College of Nutrition meeting

The 19th Annual Meeting of the American College of Nutrition will be held in Minneapolis on June 1 and 2 1978 at the Radisson South Hotel The theme for this interdisciplinary international organization this year will be Cardiovascular Diseases and Nutrition Plenary sessions will be concerned with the etiological mechanisms of nutrition inherent in cardiovascular disease primarily atherosclerosis as well as dietary drug and surgical modifications in therapy In addition the scientific paper sessions invite the submission of free communications For further information please contact Ms Faith Jermon Executive Secretary American College of Nutrition P O Box 85 669 Boston Post Road Guilford Conn 06437 or Continuing Medical Education University of Minnesota Box 293 Mayo Memorial Building 420 Delaware Street S E Minneapolis Minn 55455

Postgraduate course in Angiography and Vascular Disease

The San Diego Radiology Research and Education Foundation and the American College of Radiology will co sponsor a postgraduate course in Angiography and Vascular Disease on September 18 through 21 1978 at the Holiday Inn at the Embarcadero San Diego California

The course is designed for clinicians surgeons and radiologists interested in vascular disease An interdisciplinary approach to vascular disease will be presented integrating basic reviews and recent advances Emphasis is on interaction between angiography other diagnostic modalities recent clinical advances and therapeutic concepts For further information and registration materials please write Angiography and Vascular Disease P O Box 2763 La Jolla Calif 92038

Information for authors

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American Heart Journal

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Editorial

Ventricular afterload a succinct yet comprehensive definition

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Jules Melbin V M D Ph D
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Of the two momentous observations attributed to Starling concerned with cardiac output one was that in the heart–lung preparation with constant inflow output remained virtually independent of peripheral resistance in the physiological range In other words cardiac output was highly insensitive to afterload a term already used by Starling

The term afterload was introduced as a concept distinct from preload to distinguish phenomena relating to emptying in contrast to filling respectively of a cardiac chamber In this editorial attention is focused only on ventricular ejection and we refer only to afterload

In Starling s experiment the peripheral resistance to left ventricular ejection was controlled by adjusting the degree of collapse of a tube surrounded by air In these experiments since flow remained constant while peripheral resistance was altered arterial pressure altered proportionally with peripheral resistance Thus under such conditions peripheral resistance and arterial pressure served interchangeably as indicators of the load on the ventricle

As analysis of cardiac performance progressed to studies of the heart in situ and then to the intact heart in the conscious animal it became clear that cardiac output is in fact sensitive to afterload This was clearly demonstrated when arterial conditions were altered such that compensatory and control phenomena were avoided hence intrinsic properties of the heart were exposed

Consequently interest in afterload revived and the concept was analyzed in greater detail Conceding that peripheral resistance and arterial pressure are important factors concerned with ventricular ejection many investigators have noted that it is also affected by other circulatory variables and parameters Thus arterial compliance the inertial and viscous properties of blood and blood vessels and arterial end diastolic pressure were also attributed a role in setting the load This complexity has been further compounded with observations of interaction of contributing elements Examples include the pressure dependent characteristic impedance of the major arteries and the pressure dependent radius and compliance of the same vessels The significance of the pulse wave velocity has also on occasion been stressed Also since the load affects ejection the external work performed by a ventricle is sensitive to afterload

In the face of current confusion it is desirable to seek a comprehensive manageable definition for afterload

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The issue, however is not simple and two *fundamental concepts* relating to myocardial properties should be emphasized prior to further discussion To this end, it is convenient to utilize concepts employed with consideration of elec trical energy If a source of electrical energy operates at a constant voltage the load may be expressed in terms of the total current provided The underlying condition then is that the voltage generated by the source is independent of the current The counterpart of the voltage source is the current source If the current delivered is independent of the voltage, the voltage developed becomes a measure of the load

The properties of the heart are such that neither extreme is manifested i e ventricular pressure is neither independent of ejection flow nor is the converse true Not only are such traditional sources basically unsuitable as ana logs further complications are introduced by the presence of valves and as a consequence of conditions varying greatly with time even during a single beat Ejection flow by itself is not a qualified candidate for afterload owing to the interposition of the outlet valves Also arterial parameters, taken singly or in combination fail to qualify

The external stress, to which the myocardium is directly and continuously exposed is embodied in the intraventricular pressure Since pressure multiplied by area constitutes force ventricular pressure in conjunction with appropriate geo metric factors of the ventricle determines the forces operating to counter myocardial short ening Accordingly let us examine ventricular pressure as the variable which constitutes the ventricular afterload We shall note that all other participants which have been previously identi fied contribute to the load so defined

As a result of excitation-contraction coupling ventricular pressure rises initially without com mencement of ejection With rising ventricular pressure the load is seen to be increasing during isovolumic contraction If arterial conditions are such that the outlet valves never open (as with total occlusion at the aortic root) ventricular pressure defines the time variation in the load during the complete cycle and arterial parameters are irrelevant

Under more normal conditions the rising intra ventricular pressure soon exceeds the contin uously falling central arterial pressure from which point other factors influence afterload For convenience let us assume that mean spatial ventricular pressure and root aortic or root pulmonary trunk pressure are equal so long as the valves remain open If the ventricle were to eject into a large reservoir, which maintained the same pressure independent of blood injected by the ventricle or drained by the microcirculation ventricular pressure would rise to this level and remain there The ventricle would then experi ence an afterload which alters only during the isovolumic contraction phase Since subsequently the pressure remains constant at the level set by such an arterial reservoir, while the myocardial surface area diminishes during ejection the myocardial force may decline while ejecting against the same afterload

In the real case conditions are more complex since intracardiac pressure varies with time The time varying pressure increase ($\Delta p(t)$) at the root of the receiving artery is if linearity is assumed equal to ejection flow ($Q(t)$) also a function of time, convolved with the input impedance (Z_i) considered to be constant during a heart cycle but known to vary with heart rate * In analytical formulation, during ejection

$$\Delta p(t) = Q(t) * Z_i \quad (1)$$

Thus, arterial pressure at the aortic inlet $p(t)$ and hence ventricular pressure, $p(t)$, become, during the ejection phase

$$p(t) = p(t) = p_{(d)} + Q(t) * Z_i \quad (2)$$

where $p_{(d)}$ denotes the end diastolic root aortic pressure A similar expression applies to the inlet of the pulmonary trunk

Afterload is seen to be time variant during the entire period of systole, as a rising ventricular pressure during isovolumic contraction then during ejection by ventricular pressure according to equation 2 Afterload is thus quantified for the entire period of interest and is expressed in units of pressure or stress Where ventricular pressure differs from root aortic pressure as is possible, for example with outflow obstruction equation 2 must be modified by an additional term to accommodate such complications

Since the physical properties of the arterial system in any given state determine the value of

Input impedance of the systemic arteries is defined as the ratio between corresponding harmonics of the Fourier series of root aortic pressure and left ventricular ejection flow An analogous definition applies to the pulmonary vasculature Convolution is a mathematical procedure allowing multiplication of time dependent and frequency dependent quantities.

the input impedance (of which the total peripheral resistance is but one component) most of the quantities recommended previously as being involved with afterload find their rightful place here When the arterial system is treated as a non linear system all would be included This definition of afterload makes explicit what one would expect intuitively i e the load should vary directly with peripheral resistance and mean arterial pressure and inversely with arterial compliance

In summary a succinct general definition of ventricular afterload is proposed as the time varying ventricular pressure which incorporates previously suggested definitions as constituent elements

Echocardiographic features of the normal and malfunctioning porcine xenograft valve

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S B San Pedro, M D
Oklahoma City Okla

Prosthetic cardiac valves have been associated with a variety of cardiovascular complications [1-3] Because of the low incidence of thromboembolic complications and since long term anticoagulant therapy is not required homograft and xenograft valves have been increasingly used in recent years [4] Glutaraldehyde preserved porcine valves have the added advantage of a decreased incidence of valve disruption [5]

The echocardiographic features of the Starr Edwards aortic and mitral prosthesis, Beall mitral valve Lillehei Kastor valve and the Bjork Shiley aortic valve have been previously described [6-9] More recently the ultrasound features of the aortic bioprosthetic valve in the mitral position were described [10] The echocardiographic features of the porcine xenograft in the aortic position have not been previously reported

We report here the echocardiographic characteristics of 23 porcine xenograft valves in the aortic or mitral position Two patients developed serious valvular dysfunction Abnormal echocardiographic patterns were seen in both

Materials and methods

Echocardiograms were performed on 30 patients with porcine xenograft valves Three patients had both an aortic and a mitral porcine valve Thus a total of 33 valves were studied Technically satisfactory studies were obtained on 23 valves (from 21 patients) i e, 70 per cent of the valves studied Fourteen aortic valves and nine mitral valves were adequately visualized The group consisted of 14 males and seven females and their ages ranged from 21 to 60 years Nineteen patients were symptomatically improved after valve replacement

Two patients with a porcine xenograft valve placed in the aortic position developed serious valvular dysfunction after valve replacement The first patient was admitted with a low output state The patient died ten days after the echocardiogram was performed Autopsy revealed a markedly dilated heart and extensive thrombus formation on the valve Six weeks after valve replacement the second patient developed staphylococcal endocarditis on the porcine valve with subsequent formation of a mycotic aneurysm of the aortic root which was confirmed by angiography and surgery

Echocardiography was performed with the patients in the supine or left lateral decubitus position An Ekoline 20 Ultrasonoscope with a 10 cm focus an 0 5 inch 2 25 MHz transducer, and a Honeywell 1856 or Electronics for Medicine DR8 recorder was used In order to record the aortic prosthetic valve the transducer was usually placed in the third or fourth interspace at the left sternal border and angulated slightly medially and superiorly or inferiorly Once the echoes from the stent of the porcine valve were clearly seen within the aortic root the recording was started and slight changes in angulation of the transducer were made until the cusps of the porcine valve were seen It should be stressed that high coarse gain and low reject settings were usually necessary to record cusp echoes whereas to

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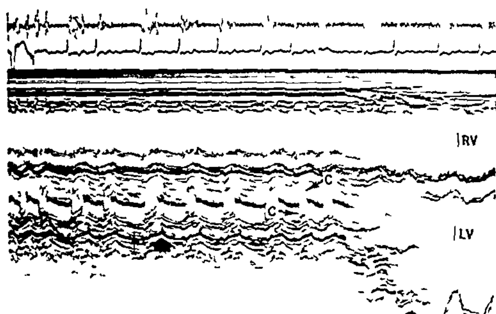


Fig 1 Sweep from aortic root to left ventricle in a patient with aortic valve replacement by a porcine xenograft valve The parallel echoes seen inside the aortic root represent the stent of the porcine valve The cusps have a box like appearance in systole In diastole a single linear echo is seen *The broad vertical arrow* points to the posterior aortic wall *The thin vertical arrow* to the left of it points to the stent C = cusp LV = left ventricle RV = right ventricle

obtain clear stent and aortic wall echoes free of secondary reverberations the reject setting of the Ekoline recorder had to be increased The thickness of the stent and the aortic wall were measured when the reverberations were eliminated by high reject setting The recording was made at 25 and 50 mm per second Prosthetic mitral valves were visualized by tilting the transducer inferiorly and laterally in the direction of the left ventricle until the stent echoes were seen Slight changes in transducer angulation enabled visualization of the cusps It is noteworthy that unlike the experience with disc and ball prosthetic mitral valves transducer placement at the apex with medial and superior angulation was not useful in obtaining xenograft mitral valve echoes The left ventricular outflow tract was measured from the anterior part of the stent to the interventricular septum

Results

Porcine aortic valve The results are summarized in Table I

The stent of the porcine valve was represented by two parallel echoes within the aortic root which had the same pattern of motion as the aorta These linear echoes were separated from

Table I Echocardiographic data of porcine xenograft valves in the aortic position

Patient	Age	Sex	Valve size (cm)	Ao Stent (cm)	Intercusp distance (cm)	Ao Stent ratio†
1	60	M	2 1	0 01	0 7	0 3
2	48	M	2 7	0.5	1 1	0 7
3	21	M	2 7	N‡	1 3	N
4	39	M	2.3	0 4	1 2	0 8
5	49	M	2 7	0 3	1 1	0 7
6	60	F	2 1	0 3	1 2	0 8
7	58	M	2 5	0 3	1.5	0 9
8	59	M	3 1	0 3	1.5	N
9	16	M	2.3	0 4	1 1	0 8
10	50	M	2 7	0 3	1 2	N
11	5[illegible]	M	2 3	0 3	1 1	0 9
12	58	M	2 7	0 3	1 1	0 9
13	52	M	2 5	0 4	1 1	0 8
14	53	M	2 7	0 3	1 5	0 8
Mean§				0 34	1 23	0 8
S D ‖				0 07	0 17	0 07
Range				0 3 0 5	1 1 1 5	0 7-0 9

Ao-Stent = distance between aortic root and stent
†Ao-Stent ratio = ratio of thickness of aortic wall to that of stent upright
‡N = technically not suitable for accurate measurement
§The mean values do not include data from patients No 1 and 3 with malfunctioning valves
‖S D = standard deviation

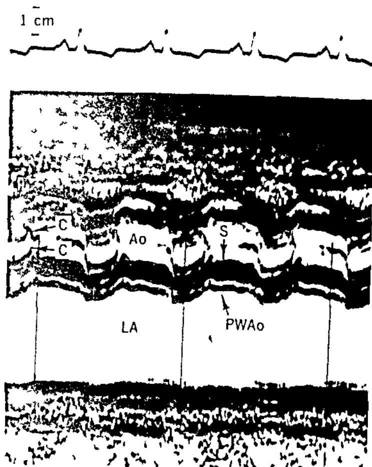


Fig 2 Echocardiogram of porcine valve in the aortic position from a patient who died 10 days later and whose autopsy showed extensive clot formation on the valve The posterior stent echo is markedly thickened (8 mm) The space between the posterior stent echo and the aortic root is markedly diminished and no space is demonstrable in systole The intercusp distance is diminished (7 mm) The anterior cusp is thickened *C* = cusp *PWAo* = posterior wall aortic root *S* = stent

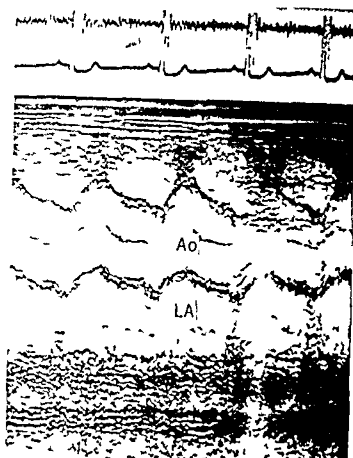


Fig 3 Preoperative echogram of a patient who developed postoperative bacterial endocarditis The maximum aortic root internal dimension is 3 7 cm *Ao* = aortic root *LA* = left atrium

the anterior and posterior wall of the aortic root respectively (in the patients who were clinically improved after valve replacement) by a distance ranging from 3 mm to 5 mm mean was 3 3 mm The cusps of the porcine aortic valve had a characteristic box like appearance in systole similar to that of the normal valve An anterior and posterior cusp which opened briskly in systole and coapted in diastole were seen In diastole, a single linear echo was present The distance between the cusps in the patients who were clinically improved ranged from 1 1 to 1 5 cm mean was 1 2 cm ± 0 15 (± standard deviation) A sweep from the aortic root to the left ventricle is illustrated in Fig 1 The two parallel echoes within the aortic root represent the stent The cusps of the porcine valve form a box like configuration in systole similar to that of the normal aortic valve A single linear echo is seen in diastole The ratio of the thickness of the aortic wall to that of the upright part of the stent ranged from 0 7 to 0 9 mean was 0 8

The echocardiogram of the patient who had thrombus formation on the valve is illustrated in Fig 2 The aortic root echoes are thin The space between the posterior stent echo and the posterior aortic root is markedly diminished and no space is demonstrable in systole The posterior stent echo is markedly thickened 8 mm and the ratio of the thickness of the aortic wall to that of the stent is decreased (0 3) compared to the other subjects The inter cusp distance is diminished (7 mm) when compared with patients with normally functioning valves The anterior cusp is thickened Another notable abnormality was that the cusp echoes were unusually prominent and were easily visible at high reject settings in contrast to the other subjects in whom a low reject setting was invariably required for adequate visualization of the cusps

The preoperative echocardiogram of the patient who developed postoperative endocarditis

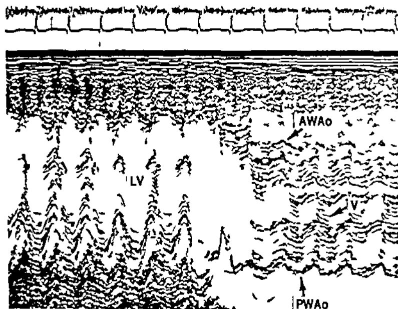


Fig 4 Echocardiogram of the patient referred to in *Fig 3* taken after the development of infective endocarditis shows marked dilatation of the aortic root (6 3 cm) There are multiple diastolic echoes in the region of the valve cusps which may represent vegetations *(V)* on the cusps *AWAo* = anterior wall of aortic root *PWAo* = posterior wall of aortic root *LV* = left ventricle

is shown in Fig 3 The aortic root dimension is 3 7 cm When compared with the preoperative record the tracing taken after the development of infective endocarditis (Fig 4) shows marked dilatation of the aortic root (6 3 cm) There are multiple echoes in the region of the valve cusps in diastole which could represent vegetations on the valve

Porcine mitral valve Fig 5 shows a sweep from the aortic root to the left ventricle in a patient with a porcine mitral valve The stent is represented by two parallel lines within the left ventricle Two cusps which open in diastole and coapt in systole are visible A single linear echo is seen in systole Another example of a porcine mitral valve is shown on Fig 6 The cusps separate in diastole to form a box like appearance A linear echo is seen between the anterior and posterior cusps This could represent the third cusp of the porcine xenograft The distance between the cusps ranged from 1 2 to 1 5 cm mean was 1 3 cm ± 0 13 The initial diastolic slope (EF slope) of the mitral valve ranged from 1 5 to 3 5 cm / second mean = 2 34 ± 0 71 (these values were obtained by averaging five beats)

Discussion

The porcine xenograft valve is similar to the human aortic valve in structure and function Fig 7 shows a photograph of a normal porcine valve The valve is mounted on a stent which has three upright parts which give rise to the parallel echoes seen on the echocardiogram The porcine aortic valve consists of three cusps which open in systole giving rise to a box like appearance and coapt in diastole resulting in a single linear echo Thus the echocardiographic appearance of the porcine valve closely resembles that of the normal aortic valve The distance between the cusps however is less than that observed in a group of normal subjects studied in our laboratory In the patients with normally functioning porcine valves the intercusp distance ranged from 1 1 cm to 1 5 cm mean was 1 2 cm ± 0 15 whereas in normal subjects the intercusp distance ranged from 1 5 cm to 2 4 cm with a mean of 1 8 cm These data suggest that aortic valve orifice of the porcine valve is smaller than that of the normal human aortic valve A recent report by Morris and associates[1] pointed out that there was an average peak systolic gradient of 23 mm Hg at rest and 37 mm Hg during exercise across porcine aortic valves The calculated valve area[1] ranged from 0 75 to 1 67 square centimeters Their results are consonant with our finding of smaller cusp excursion in the porcine valve group

The two patients who developed clinically significant valvular dysfunction had abnormal

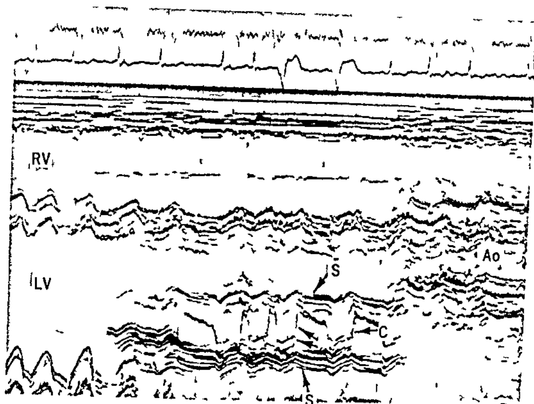


Fig 5 Echocardiogram which shows a sweep from the aortic root *(Ao)* to the left ventricle in a patient who had porcine valve replacement of the mitral valve The stent is represented by two parallel lines within the left ventricle *(LV)* The cusps *(C)* open in diastole and coapt in systole producing a single linear echo *RV* = right ventricle *S* = stent

Table II Ultrasound measurements of xenograft valves in the mitral position

Patient	*Age*	*Sex*	*Valve size (cm)*	*Inter cusp distance (cm)*	*LVOT**		*Valvar diastolic slope (cm/sec)*	*Septal motion*
					ED (cm)	*ES (cm)*		
1	48	M	3 1	1 2	2 7	2 4	1 9	P
2	38	F	2 5	1 5	1 8	1 8	1 5	P
3	51	F	2 5	1 3	3 0	2 0	2 3	N
4	58	F	2 3	1 2	1 6	1 3	1 9	P
5	24	F	2 7	1 3	1 3	1 0	3 5	P
6	60	F	2 3	1 2	1 5	1 4	1 5	P
7	59	M	3 1	1 5	1 6	1 2	3 0	P
8	16	F	2 9	1 2	1 0	0 8	3 0	P
9	60	F	2 7	1 2	2 2	2 0	2 5	P
Mean				1 3	1 9	1 54	2 34	
SD				0 13	0 66	0 53	0 71	
Range				1 2 1 5	1 0 3 0	0 8 2 4	1 5 3 5	

Abbreviations LVOT = left ventricular outflow tract ED = end diastole ES = end systole P = paradoxical N = normal

echocardiograms Extensive clot formation on the valve was noted at autopsy on the first patient The posterior part of the stent was markedly thickened, the distance between the posterior stent and the posterior aortic root was markedly reduced, the intercusp distance was reduced the cusp echoes were unusually prominent and the anterior cusp was thickened The postoperative course on the second patient was complicated by bacterial endocarditis affecting the porcine valve and formation of a mycotic aneurysm of the aortic root Dense echoes were noted in diastole in the region of the porcine valve These could have represented vegetations on the valve A striking change in aortic root diameter when compared with the preoperative dimension indicated the recent development of an aneurysm The formation of a mycotic aneurysm of the aortic root is an unusual, but ominous complication of prosthetic valve endocarditis Serial echo

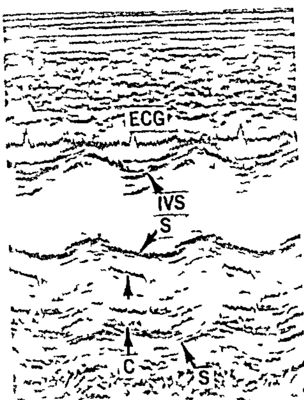


Fig 6 Echocardiogram of a patient who had porcine valve replacement of the mitral valve The stent is represented by two parallel lines inside which are the cusps *(C)* The cu ps open in diastole producing a box like configuration A third linear echo is seen between the anterior and posterior cusp *(arrow)* which may represent a third cusp The cusps coapt in systole producing a linear echo *S* = stent *IVS* = interventricular septum

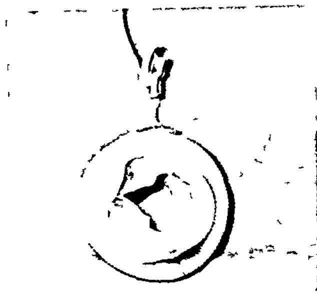


Fig 7 Photograph of a normal porcine xenograft valve The stent has a base and three upright projections The three cusps of the valve are seen in the open position

cardiography of the aortic root in patients with infective endocarditis may prove to be of value in the early detection of this serious complication The above example points to the usefulness of a baseline ultrasound tracing in patients with prosthetic porcine valves If a technically satisfactory tracing is obtained shortly after valve replacement the development of a complication such as infective endocarditis clot formation on the valve or aneurysm formation can be made with a much greater degree of confidence than if a baseline tracing was not available

Porcine aortic xenograft replacement of the mitral valve results in a tricuspid left atrioventricular valve The echocardiographic appearance of this valve was similar to that of the porcine aortic valve Two parallel lines which represented the stent were seen within the left ventricle An anterior and posterior cusp which produced a box like appearance in diastole were seen The coaptation of the cusps in systole resulted in a single linear echo The intercusp distance ranged from 1 2 to 1 5 cm mean was 1 3 cm This distance is considerably less than that found in a group of normal subjects studied in our laboratory (intercusp distance ranged from 2 8 to 3 2 cm mean was 3 0 cm) These data suggest that the orifice of the porcine valve in the mitral position is smaller than that of the human mitral valve Our thesis is supported by the report of Johnson and associates[12] who found diastolic gradients across the mitral valve in all fourteen patients who were catheterized following mitral valve replacement with a porcine xenograft The calculated valve area ranged from 0 92 cm to 3 39 cm and the average was 2 15 cm [2,12] It is interesting that unlike the normal mitral valve the porcine mitral valve had a reduced EF slope Thus some morphological changes such as flattening of the EF slope which are used in diagnosing stenosis of the normal mitral valve will be of limited value in diagnosing porcine valve stenosis In a recent report Horowitz and associates[13] described calcific homograft stenosis which was characterized by increased echo density from the tissue leaflets and thrombus formation on the sewing ring which was associated with decreased leaflet excursion and decreased ratio of internal to external stent diameter [3] Horowitz and associates also studied a group of patients with

normally functioning bio prosthetic valves in the *mitral position* The dimensions for the left ventricular outflow tract that they obtained were similar to those seen in our patients The inter cusp distance in their group was slightly greater than the figures obtained in our study This was probably because the prosthetic valve size was in general smaller in our group of patients

In summary the echocardiographic features of the mitral and aortic porcine xenograft valve are presented Two patients developed serious com plications Both had abnormal echocardiograms Echocardiography may prove to be a useful tool in the follow up of patients with porcine valves and in the detection of early prosthetic malfunc tion

Summary

Echocardiograms were performed on 33 pros thetic porcine valves Satisfactory tracings of the valve were obtained in 23 (70 per cent) The characteristic appearance of the porcine aortic prosthesis consisted of two lines parallel to each other within the aortic root, which had the same pattern of motion as the aortic root These lines probably represented the stent of the porcine valve The valve cusps had a characteristic box like appearance in systole similar to that of the normal aortic valve A single echo was seen in diastole The distance between the cusps in systole in patients who were clinically improved after valve replacement ranged from 1 1 cm to 1 5 cm with a mean of 1 2 cm This distance is less than that observed in a group of normal subjects studied in our laboratory range 1 5 to 2 4 cm mean 1 8 cm Two patients developed clinically significant valvular dysfunction The first patient had dense echoes on the anterior cusp and the stent and reduced intercusp distance He died ten days later and extensive thrombus formation on the porcine valve was noted The second patient developed infective endocarditis of the porcine valve and a mycotic aneurysm of the aorta Multiple diastolic echoes were seen in the region of the porcine valve and marked enlargement of the aortic root (6 3 cm) when compared with the preoperative record (3 7 cm) was noted

The stent of the porcine mitral valve was represented by two parallel echoes in the left ventricular cavity The valve cusps had a box like configuration in diastole similar to the normal aortic valve The distance between the cusps ranged from 1 2 cm to 1 5 cm mean was 1 3 cm

Unlike the normal mitral valve motion of the valve in diastole was flat and the characteristic M shaped complex was not present In summary, echocardiography may prove to be a useful tool in the assessment of the normal and malfunctioning prosthetic porcine xenograft valves

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Arrhythmias and the 'Holiday Heart': Alcohol-associated cardiac rhythm disorders

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An association between alcohol use and cardiac arrhythmias, particularly atrial fibrillation, has long been suspected.[1] However, the specific etiologic role of alcohol is difficult to establish and indeed doubt may exist as to the presence of any heart disease when overt cardiomyopathy is not present. Recent observations in our laboratory and by others have indicated that acute and chronic alcohol ingestion leads to demonstrable depression of myocardial function in animals and man,[*] and that cardiac conduction abnormalities and morphologic changes may result as well.[1]

Between January 1972 and January 1976 we observed or reviewed 32 separate dysrhythmic episodes requiring hospitalization in 24 patients who drank heavily and habitually with superimposition of especially heavy ingestion prior to the arrhythmia. Overt alcoholic cardiomyopathy was not present; the group was selected only insofar as all patients drank heavily, had arrhythmias, and had normal or borderline heart size (by x-ray) and normal or borderline ECG's after return to sinus rhythm. The clinical and physiological characteristics of these patients, the spectrum of their arrhythmias and treatment, and the unusual temporal distribution of the arrhythmias form the basis of this report.

Methods

All but one patient were seen at two hospitals visited by one of us (P. O. E.). At Martland Hospital, the major teaching hospital of the New Jersey Medical School at Newark, N. J., serving an economically depressed area, 18 patients (25 admissions) were evaluated. At Englewood Hospital, Englewood, N. J., a community hospital located in a prosperous suburban region, five patients (five admissions) were observed. One typical patient admitted to another local hospital and later studied by us was included, and a prior alcohol-associated arrhythmia in a distant hospital by another patient is also included. Most patients were seen in referral from other physicians at the two hospitals; no attempt was made to survey retrospectively all hospital admissions for arrhythmias, as a connection between alcohol ingestion and rhythm disturbance was rarely made prior to consultation with us. All patients seen by us during this period who satisfied the criteria of alcohol-associated arrhythmia, normal ECG and chest x-ray, and no clinical evidence of heart disease were included.

Arrhythmias were the reason for admission in 30 instances, manifested by palpitations, precordial pressure, sharp left chest pain, or passing

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out spells History was often sketchy Two patients came to the hospital with fibular fractures consequent to being injured while intoxicated Neither had head or chest injuries, nor was a history of trauma obtained from any other patient

Initial ECG s and chest x rays were obtained in all and ECG s were repeated daily Arterial and venous blood was taken on admission for arterial gases, pH, CBC, electrolytes, LDH urea, glucose cholesterol, and SGOT Blood alcohol was measured in eight patients Treatment was at the discretion of the admitting physician, all patients survived Later, the day of the week on which each admission occurred as well as the monthly distribution was analyzed statistically The latter was compared with monthly hospital totals for other, traditionally accepted alcohol associated illnesses (including delirium tremens acute and chronic alcoholism, alcoholic psychosis, episodic and habitual drinking alcoholic addiction, and Laennec s cirrhosis) obtained by review of hospital discharge diagnoses between January, 1971, and December, 1974

To exclude overt cardiomyopathy or other cardiovascular disorders, only patients without x ray evidence of cardiac enlargement and with normal or borderline ECG s after return to normal rhythm were included No patient had angina, history of rheumatic fever or murmur, myocardial infarction, peripheral vascular disease, diabetes or hyperlipidemia One was moderately obese None had any murmur extra heart sound, or apical thrust on physical examination One had mild chronic hypertension (BP 160/90) in several the admitting blood pressure was elevated but returned quickly to normal A qualitative and quantitative history of alcohol use was obtained by intensive questioning of each patient and where available other family members Later we attempted to evaluate all patients further although several signed out of the hospital early or failed to return for scheduled studies

Systolic time interval measurements (preejection period [PEP] left ventricular ejection time [LVET] and their ratio [PEP/LVET]) were made in the postabsorptive state in 17 of the 24 patients at least three days after return to sinus rhythm All medication had been stopped at least 48 hours earlier The systolic time intervals were measured using the method and instrumentation described by Weissler and colleagues[12, 13] from simultaneously recorded ECG's, phonocardiograms, and carotid pulse tracings recorded photographically at paper speeds of 150 or 200 mm /sec with time markers at 0 02 sec Ten complexes were measured for each subject Total electromechanical systole (Q S) and left ventricular ejection time (LVET) were measured directly and the PEP was calculated by subtraction ([Q S] – [LVET]) The ratio PEP/LVET was derived for each patient and a mean ratio was calculated for the group, the mean PEP/LVET ratio was compared with that of 17 normal age matched subjects Because of heart rate differences corrected values for PEP (PEPI) and LVET (LVETI) in milliseconds were obtained using the following regression formulas PEPI = PEP (measured) + 0 40 × HR for women, PEPI = PEP (measured) + 0 41 × HR for men, LVETI = LVET (measured) + 1 6 × HR, for women, LVETI = LVET (measured) + 1 7 × HR for men

High speed (200 mm /sec) high frequency (0 1 to 2 000 Hz) recordings of standard ECG limb leads were obtained at the same time Heart rate PR interval, QRS duration, and QT intervals were each measured in the three leads and the longest duration of each was taken at the true duration PR and QT were corrected for rate by dividing each by the square root of the preceding R R interval A group of ten age and sex matched normal persons without arrhythmia or drinking history were studied during the same period for comparison

In order to rule out significant coronary artery disease and evaluate left ventricular performance eleven patients were studied by diagnostic right and left heart catheterization at intervals of one to four months following the dysrhythmic episodes Intracardiac pressure data recordings, cardiac outputs by dye-dilution left ventriculography selective coronary arteriography and His bundle electrography were performed in all In eight patients an additional catheter was placed in the aortic root so that dye-dilution measurement of left ventricular volume and ejection fraction could be obtained by injecting indocyanine green dye into the left ventricle and sampling from the aortic root using methods previously reported[14] Five patients had duplicate measurements of left ventricular end diastolic pressure and stroke index at rest and then during

intravenous infusion of a dilute solution of angiotensin.[5] For the latter measurements were made during the tenth to twentieth minutes following elevation of the aortic diastolic pressure by about 15 to 20 mm Hg. In all cases hemodynamic measurements were completed prior to or at least 45 minutes after angiography. Hemodynamic data in the alcoholic subjects was compared with that obtained in a selected group of 12 normal persons studied in our laboratory; eight normals underwent angiotensin testing.

Comparisons between alcoholic and normal groups were made utilizing Student's t test for unpaired mean data. Chi square analysis was used in the evaluation of admitting day, making the assumption that Sunday through Tuesday admissions should have been only 3/7 of the total.

Illustrative cases

Case 1 J. McC., a 69 year old doorman, lived alone and drank heavily. During December 1971 he received many bottles of liquor from the tenants of the apartment house where he worked. He worked on New Year's Eve but drank upon returning home; he fell asleep but awoke with precordial pressure and palpitations and at 2 A.M. on January 1, 1972 was brought to the hospital emergency room. Atrial fibrillation with a rapid ventricular response was seen. K was 2.7 mEq./L. Treatment with digoxin was begun and the rhythm converted to RSR. He was lost to follow up after discharge.

Case 2 D. R., a 39 year old business man, spent a long weekend drinking heavily in a motel. After three days he developed palpitations and on Tuesday, September 30, 1969 he was seen at another hospital with atrial fibrillation and was cardioverted. He felt well but gradually resumed consumption of 12 to 15 cans of beer daily. Four years later, on Wednesday, October 10, 1973 he presented at the hospital emergency room with palpitations. Frequent atrial extrasystoles (with LBBB aberration) were treated with quinidine. Plasma electrolytes were normal. Since reducing his beer consumption and continuing quinidine, palpitations have lessened although he has frequent palpitations when he drinks more heavily.

Case 3 M. H., a 31 year old woman, drank whiskey in quart quantities daily. On Thursday, December 27, 1973 she was seen at the hospital emergency room because of palpitations and breathlessness; atrial fibrillation with ventricular extrasystoles was present. Within minutes the rate accelerated with runs of beats of uncertain origin, possibly ventricular tachycardia. Cardioversion was performed immediately. Plasma electrolytes were normal. In the next two years she was admitted on three additional occasions, each time with atrial fibrillation and the same drinking history. One each occurred on a Sunday, Monday, and Tuesday.

Case 4 W. K., a 43 year-old businessman, consumed at least six oz. of martinis daily for many years. During December 1974 he had additional liquor at business luncheons. On Monday, December 30, 1974 he "passed out" while seated in a cinema and was taken to the hospital emergency room. Frequent ventricular extrasystoles were present and the plasma K was 2.7 mEq./L. Treatment with procainamide and K suppressed the arrhythmia. Three weeks later, while asymptomatic and arrhythmia free at rest, an exercise stress test induced ventricular extrasystoles and runs of ventricular tachycardia after the exercise and this arrhythmia was presumed to be the basis of his presenting symptoms. With abstinence and outpatient treatment with quinidine, the arrhythmia has not recurred.

Results

Clinical data Twenty patients in our series were male and four female (aged 25 to 62 years, mean 43 years). All but three were between 30 and 60 years old; eight patients were in the fourth decade, seven in the fifth, and six in the sixth decade; all gave histories of consuming at least 6 to 10 drinks daily. A history of at least ten years of heavy ethanol consumption was usually present as a background. All varieties of beer and whiskey were implicated, alone or in combination. Most patients drank every day of the week but indicated that weekend consumption was higher. We have not yet observed this disorder in anyone who drank wine alone, although this may be a cultural difference inasmuch as wine drinkers are less frequent in our population than whiskey or beer drinkers. All but two patients smoked heavily.

Following resolution of the arrhythmias, most patients were asymptomatic, although one developed overt alcoholic hepatitis and two had delirium tremens. None of these three were further studied. Low plasma potassium, previously implicated as a possible cause of arrhythmias in alcoholics[?] and of arrhythmias and conduction disturbances in general,[7] was less than 3.5 mEq./L in only four of 30 instances, although a whole body potassium deficit was not excluded. SGOT was usually normal or borderline elevated. Blood alcohol determinations were performed on admission in eight patients and were positive in six, ranging from 50 to 430 mg. per cent. Plasma sodium, chloride, bicarbonate, lactic dehydrogenase, urea, sugar, and cholesterol were normal. Arterial blood gases and pH were normal in all. Plasma magnesium was not measured.

Fig. 1 indicates the admitting day of the week in each instance. Nineteen patients were initially seen between Sunday and Tuesday, with Monday admissions most common. By chi square testing 19 of 32 episodes occurring on three of the seven days of the week is significantly greater than the

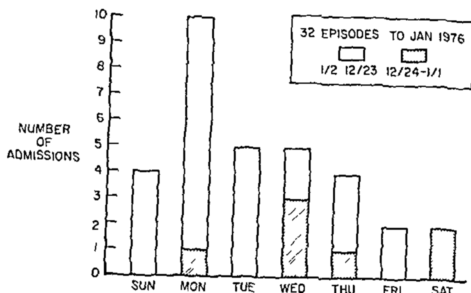


Fig 1 Admitting day for alcoholic arrhythmias Nineteen admissions were seen Sunday through Tuesday (post weekend) Of the 13 Wednesday through Saturday admissions six were during the year end holidays Therefore 25 of 32 admissions were holiday related

Table I ECG and chest x rays in Holiday Heart patients

Electrocardiograms (total 24)	
Fully normal	16
Normal except LAD −10 to −30	4
Normal except P wave 0 12 sec	2
T waves low (not flat) 1 2 leads (one of these also showed first degree A V block)	2
Chest roentgenograms (total 24)	
Fully normal	21
Cardiothoracic ratio 50%	3

Table II Alcohol associated arrhythmias*

Rhythm abnormality	*No*
Isolated APCs	4
Atrial fibrillation	12
Atrial flutter	6
Paroxysmal atrial tachycardia	3
Junctional tachycardia†	4 (3 in 1 patient)
Isolated PVCs	6
Ventricular tachycardia	1 (after treadmill exercise)

*Several patients had more than one arrhythmia Of atrial arrhythmias 6 showed RBBB and 3 LBBB aberration
†One patient with junctional tachycardia showed atrioventricular dissociation

3/7 expected, $P < 0.05$ Further examination of the data is even more striking, as six of the 13 admissions from Wednesday through Saturday were seen between December 24 and January 1 If these six holiday admissions are added to the 19 post weekend admissions, then fully 25 of the 32 episodes could truly be considered examples of a holiday heart syndrome a name which has been used at our institutions to describe them

In Fig 2, the number of alcoholic arrhythmia admissions per month over the four year period is shown Only two patients were seen between May and August while the incidence peaked in December and January In the bottom graph the mean combined monthly incidence of hospital admissions for all other traditionally accepted alcohol associated illnesses are tabulated for comparison in three years of the four year period These other illnesses did not fall into any seasonal pattern

Electrocardiographic and x ray data ECGs in 16 patients were fully normal after resolution of arrhythmia (Table I) whereas four showed mild left axis deviation (up to −30 degrees) two were normal except for a broad P wave and two had minimal T wave abnormalities Many had transitory post conversion ECG abnormalities with evidence of atrial and/or ventricular extrasystoles ST T abnormalities and QT prolongation but the tracings returned to normal within 48 hours Some patients were observed to show diminutive or absent Q waves in ECG Leads I and V_6 (absent septal Q) a finding previously reported to be common in cardiomyopathy[18] However these were not possible to compare quantitatively with normals because of differences in technical quality of the electrocardiograms which were examined retrospectively

Routine chest x rays indicated normal cardiac

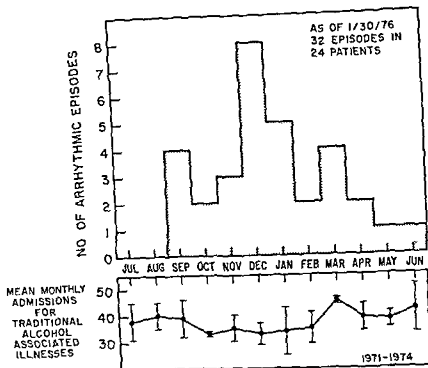


Fig 2 Monthly distribution of holiday heart hospital admissions (top) compared with mean monthly admissions for traditional alcohol associated illnesses (bottom) The apparent year end peak of alcoholic arrhythmias is not present for the traditional" alcoholic illnesses

size in 21 (cardiothoracic ratio < 50 per cent normal appearing silhouette) The cardiothoracic ratio was 50 per cent in three patients

Arrhythmias observed The most commonly seen arrhythmia was atrial fibrillation followed by atrial flutter and isolated ventricular premature beats (Table II) The latter were especially common in association with atrial fibrillation when the ventricular rate was rapid Several patients each had isolated multiple supraventricular beats and paroxysmal atrial tachycardia Four episodes of junctional tachycardia were observed—three in one patient and a fourth associated with transient atrioventricular dissociation in another person During arrhythmia six instances of right bundle branch block type aberration and three of the left bundle branch block type were observed but several of these occurred at rapid ventricular rates Consequently it was not possible to describe aberration quantitatively although it was present unexpectedly in some patients at relatively slow rates

Medical treatment of arrhythmias Treatment of all patients was usually begun in the emergency room no protocol was followed Digoxin was used most commonly although cardioversion pressor infusions quinidine procainamide and carotid massage were all employed Eight episodes went untreated and resolved spontaneously All patients survived

Systolic time intervals The mean PEP/LVET ratio in the alcoholics 0 412 ± 0 014 was significantly different from that obtained in the age matched controls 0 299 ± 0 008 P < 0 001 (Fig 3) The measured mean PEP was longer and the mean LVET shorter in the alcoholics Because of heart rate differences (the mean heart rate of the alcoholics during systolic time interval testing was 82 ± 3 BPM and of normals 67 ± 2 BPM P < 0 001) PEP alone and LVET alone were not directly comparable However when corrected for heart rate (PEPI and LVETI) the mean PEPI was indeed longer (136 ± 3 msec in alcoholics 116 ± 3 msec in controls P < 0 001) and mean LVETI shorter (383 ± 7 msec in alcoholics 407 ± 3 msec in controls P < 0 005) in the alcoholic group

High speed electrocardiographic data Results of high speed electrocardiographic measurements of PRc QRS duration and QTc are shown in Table III The mean for alcoholic patients measured 17 per cent higher for PRc 23 per cent

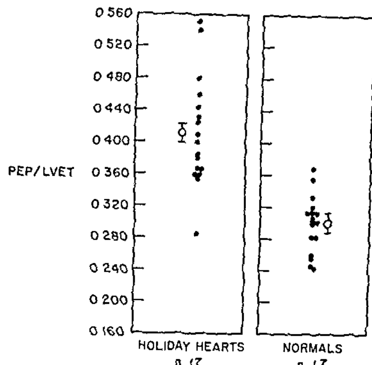


Fig 3 Systolic time interval ratios (PEP/LVET) in patients with arrhythmias *(left)* and in normals *(right)*. *Filled circles* are individual data points, means are *open circles* and standard errors are shown

higher for QRS, and 14 per cent higher for QTc in comparison with normals

Cardiac catheterization data Mean cardiac index was significantly lower in the alcoholic group (2 6 ± 0 2, normals 3 3 ± 0 2 L/minute P < 0 05) However other measurements including mean left ventricular end diastolic pressure and volume indices mean stroke volume index mean end systolic volume index mean ejection fraction, and mean velocity of contractile element shortening did not differ significantly from normal Nevertheless four patients had left ventricular end diastolic pressures in excess of 12 mm Hg (up to 20 mm Hg) and in all data categories the mean differences from normal varied in a direction consistent with abnormality (The mean heart rate at the time of study in our catheterized normal group was 80 BPM while in the alcoholic group it was 67 BPM thus accounting for a low mean cardiac index in the alcoholics with a normal mean stroke volume index)

During the angiotensin infusions aortic diastolic pressure rose 17 mm Hg in the alcoholic group and 21 mm Hg in normals Left ventricular end diastolic pressure rose significantly and equivalently (alcoholics 8 0 ± 1 3 to 12 0 ± 2 3 mm Hg normals 6 3 ± 0 6 to 10 0 ± 0 5 mm Hg) in both groups and the mean values in both states were not significantly different in the two groups Stroke volume index, however did not change in the alcoholics (38 5 ± 2 3 to 36 1 ± 1 4 ml/beat/M²), while in the normal group it rose significantly (38 4 ± 2 9 to 45 5 ± 3 1 ml/beat/M², P < 0 02 for intergroup comparison) The inability to increase stroke volume with rising end diastolic pressure is considered further evidence of left ventricular dysfunction

Selective coronary arteriograms and left ventriculograms were normal in all 11 patients studied, the mean H V time, 42 ± 2 msec, was normal as well

Table III P QRS T durations from high speed ECG

	"Holiday Hearts (N = 17)	Normals (N = 10)	P
PRc (msec)	179 ± 7	153 ± 6	< 0 01
QRS (msec)	98 ± 3	80 ± 2	< 0 001
QTc (msec)	430 ± 9	377 ± 6	< 0 001
Heart rate (BPM)	82 ± 3	63 ± 3	< 0 001

One patient had first degree A V block and is excluded from PRc measurements

Discussion

The 24 patients included in this study each gave a similar history of prolonged heavy alcohol use with recent superimposition of more intensive weekend or holiday drinking Cardiac arrhythmias developing in these circumstances are in our experience, often misdiagnosed as idiopathic as no clinical evidence of heart disease remains after resolution of the rhythm problem and the extent of alcohol use may be unrecognized Because of the rather typical weekend or holiday presentation we have called this the holiday heart syndrome, which we define as an acute cardiac rhythm and/or conduction disturbance associated with heavy ethanol consumption in a person without other clinical evidence of heart disease and disappearing without evident residual with abstinence Our report details numerous atrial and ventricular arrhythmias and one instance of transitory atrioventricular block The unusual seasonal peak at year end and early in the New Year corresponds to the known peak of liquor sales at that time [19]

While the year end and the post weekend

tendency toward arrhythmias is clear in these heavy drinking patients it is not clear why similar disturbances are not seen in proximity to the July 4 and Labor Day holidays Dilution of the alcohol during the summer with other liquids may prevent rapid absorption thus preventing excessive blood levels from developing

The mechanism by which these arrhythmias occur is not known Conduction and rhythm disturbances are common in overt alcoholic cardiomyopathy [2] bundle branch block atrioventricular block atrial and ventricular arrhythmias have all been reported Alcoholic excess may be accompanied by malnutrition and effects of malnutrition or associated coronary artery disease or electrolyte disturbances have been difficult to exclude In recent investigations from our laboratory chronic conduction abnormalities including H V and QRS prolongation were induced in otherwise healthy and well nourished dogs that drank ethyl alcohol in quantity for longer than one year [1] In these animals infiltration of the myocardial interstitium with Alcian Blue positive material and electron microscopic evidence of intercalated disc disruption were observed either of which alteration could have been responsible for prolonged conduction Cardiac hypertrophy was not present Cardiac conduction delays are believed to play an important role in arrhythmia production by facilitating reentry [2] While the PR QRS and QT prolongations observed in the current series of patients are modest it is possible that more severe localized areas of delay are present Indeed histologic evaluation of the heart in human cardiomyopathy and after alcoholic ingestion by animals emphasize a variable patchy distribution of lesions

The acute effects of alcohol on the ECG are only seen with serum levels above 600 mg /100 ml or more respiratory arrest with hypoxia may predispose to arrhythmias under these conditions [1] We have previously shown that isolated ventricular ectopic beats may occur only 1½ to 2½ hours after the onset of moderate alcohol administration however Ethanol shortens atrial muscle refractory period [2] which might induce atrial arrhythmias but the serum alcohol concentrations required are much higher than those observed in alcoholic man The patients we studied were usually seen during or immediately after a drinking episode Some of the arrhythmias actually began at a time of intoxication although some patients recalled onset of palpitations as an abrupt event occurring when they were not intoxicated Nevertheless the odor of ethanol was apparent at the time of admission in many and serum alcohol levels were elevated in most cases in which they were obtained While the outcome in our patients was benign the very rapid rates observed in several suggested that the result might not have been salutory outside the hospital such arrhythmias might be a cause of the sudden death commonly reported in alcoholics [28]

Evidence for mild left ventricular dysfunction in this group was not unexpected As early as 1969 reports from this laboratory and others showed that preclinical cardiac dysfunction in apparently noncardiac chronic alcoholics could be demonstrated [8, 11, 29, 0] We believe that a preclinical cardiomyopathy is present in the majority of these patients Although we have not yet observed the transition to overt cardiomyopathy in any patient perhaps because of the limited period follow up in at least three patients a diagnosis of a possible cardiomyopathy might be entertained because of borderline cardiomegaly

While this report deals specifically with arrhythmias occurring in chronic drinkers it appears that alcohol is occasionally able to precipitate similar disturbances in persons who do not admit to habitual alcohol use We observed one episode of atrial fibrillation (on New Year s Eve) in a 52 year old otherwise healthy woman who insisted that she had taken only one cocktail a few hours earlier Too little data is available now regarding this particular subgroup but it deserves further study

Summary

An association between excessive alcohol use and cardiac rhythm disorders is often difficult to establish in the absence of overt cardiomyopathy We studied 32 separate hospital admissions for dysrhythmias in 24 patients (20 men 4 women) with heavy recent alcohol ingestion and prolonged excessive alcohol use None had evidence of overt heart disease after treatment of arrhythmia Episodes usually followed heavy weekend or holiday sprees resulting in hospitalization between Sunday and Tuesday or in proximity to the year end holidays a relationship not observed in other alcohol associated illnesses Atrial fibril

lation was most common, but atrial flutter atrial tachycardia junctional tachycardia multiple APC's, multiple PVC's and ventricular tachycardia were also observed Transient hypokalemia was present in four of 30 The mean PEP/LVET ratio after treatment was 0 412 ± 0 014 (normal 0 299 ± 0 008, $P < 0\ 001$) High speed ECG's showed prolongation of PRc QRS and QTc At cardiac catheterization intracardiac pressures and volumes coronary arteriograms and ventricular wall motion were normal at rest and mean cardiac index was slightly low, but the left ventricular response to angiotensin was abnormal Cardiac arrhythmias presenting during weekend or holiday drinking episodes are associated with conduction delays and depressed cardiac performance indicative of early cardiomyopathy and suggest a holiday heart syndrome

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Angina pectoris myocardial infarction and sudden cardiac death with normal coronary arteries A clinicopathologic study of 9 patients with progressive systemic sclerosis

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Generally ischemic heart disease can be ascribed to lesions of the epicardial coronary arteries[1] Although uncommon the occurrence of angina pectoris myocardial ischemia and necrosis and/or sudden cardiac death with angiographically normal coronary arteries has been the subject of considerable interest and speculation[3 1] but autopsy documentation of this entity is generally lacking and its etiology remains obscure Kemp and associates[2] have suggested the possibility of regional functional arterial or arteriolar constriction but without supporting evidence

It has been recognized for many years that progressive systemic sclerosis (PSS) may be associated with myocardial fibrosis and in 1943 Weiss and colleagues[5] noted the peculiarity of myocardial scars in patients without associated coronary artery disease The functional significance of the myocardial lesion in PSS as well as its etiology however have been the subject of controversy It has been suggested that the fibrosis in the heart as well as elsewhere in the body in PSS is due to abnormal collagen proliferation[5] and some have claimed that the myocardial abnormalities are mainly secondary to severe renal and pulmonary disease[17] Another possible explanation is that an underlying vasomotor abnormality accounts for systemic hypertension and renal disease[9] pulmonary hypertension[15] and the myocardial disease[20] of PSS

This report describes ischemic myocardial disease associated with angina pectoris arrhythmias myocardial necrosis and/or sudden death in nine patients with morphologically normal coronary arteries who had progressive systemic sclerosis and Raynaud s phenomenon The pattern of necrosis in these patients suggests a myocardial Raynaud s phenomenon as one possible pathophysiologic mechanism of ischemic heart disease with morphologically normal coronary arteries

Methods

We recently studied morphologic features of the myocardial disease associated with PSS in the first 52 patients with this disease autopsied at The Johns Hopkins Hospital and found that an unexplained myocardial lesion was present in approximately half of them[20] Since that time three additional patients have been studied including a 12 year old child who died of a myocardial infarct with morphologically normal coronary arteries The striking clinical presentation of acute myocardial infarction and sudden death in a young girl led us to review the other patients with progressive systemic sclerosis who had clinical evidence of ischemic heart disease but morphologically normal coronary arteries

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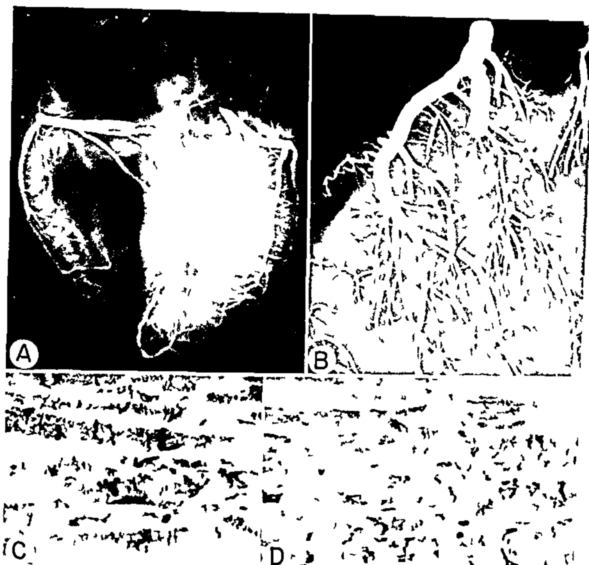


Fig 1 Postmortem angiogram (*A*) and microangiogram (*B*) of the heart of a 12 year old girl (Case No 1) who died during an episode of Raynaud s phenomenon Epicardial and intramural coronary arteries were widely patent by angiography and light microscopy *C* Extensive necrosis of the contraction band type was present throughout right and left ventricles as shown in this photomicrograph from a central portion of a focal lesion in the left ventricle *D* Margin of another focal lesion with unaffected muscle cells at upper left (*B* original magnification ×7½ *C* and *D* phosphotungstic acid hematoxylin stain original magnifications ×600 and ×500)

Of 55 autopsied patients with progressive systemic sclerosis 50 had widely patent coronary arteries Of this latter group nine had clinical and pathologic evidence of ischemic myocardial disease including angina pectoris myocardial necrosis and sudden cardiac death but morphologically normal coronary arteries Sudden death was defined as death within six hours of onset of symptoms These nine patients form the subject of this report

Clinical and autopsy records were reviewed in each of the nine patients In each patient gross specimens of heart were reexamined and histologic sections of lung kidney upper and lower gastrointestinal tract skeletal muscle and skin were examined In addition a minimum of 5 and an average of 50 histologic sections of myocardium were examined from each heart Epicardial coronary arteries from each patient were examined by multiple transverse sections at approximately 5 millimeter intervals in the nine patients and in addition by barium sulfate postmortem angiography in one (Case No 1) In the latter case microangiograms were prepared from tissue blocks of both ventricles and examined by light microscopy (Fig 1) to assess the microvasculature

Results

Clinical observations The nine patients ranged in age from 12 to 70 years (average 44 years) and six were women In eight patients the diagnosis of

PSS was made during life by skin and/or esophageal abnormalities In one patient (Case No 1) the 12 year old girl non specific muscular complaints and progressively severe Raynaud s phenomenon were present for 18 months before death but the diagnosis of PSS was not made until autopsy Clinically severe restrictive lung disease had been present in two patients (Cases No 6 and 9) for several years Renal dysfunction was evident in only one patient (Case No 7) and in her led to acute renal failure and death Two of the nine patients (Cases No 4 and 5) had systemic hypertension In all nine patients Raynaud s phenomenon was present and in two patients (Cases No 1 and 9) was of increasing severity over several days immediately prior to their sudden death Chest pains of unknown cause were present in six patients and in three the diagnosis of angina pectoris was made and confirmed by an exercise stress test or ischemic ST T wave changes on electrocardiogram during pain None of the patients underwent cardiac catheterization Electrocardiograms were abnormal in all nine patients showing non specific ST T wave changes in five right bundle branch block (associated with pulmonary PSS) in two premature ventricular contractions in six including ventricular bigeminy in three and runs of ventricular tachycardia in one In two patients a 54 year old woman (Case No 9) and the 12 year old girl (Case No 1) transient ST segment elevations were noted during an episode of chest pain at rest in the former and immediately prior to death in the latter Ischemic ST changes arrhythmias and/or chest pains shortly before death led to the clinical impression that sudden death was due to an acute myocardial infarction in four patients (Cases No 1 2 3 and 8) In four others with a history of multiple premature ventricular contractions sudden death was thought to be related to the ventricular arrhythmias (Cases No 4 5 6 and 9) One patient with a history of well documented angina pectoris died of renal failure sepsis and congestive heart failure Since a seasonal relationship to mortality in PSS has been observed the time of year that each patient died was reviewed and is indicated in Table I Of the eight patients dying suddenly four died in the fall or winter months and four in June or July The other patient died of renal failure in July

Autopsy findings At autopsy the diagnosis of PSS was confirmed by typical PSS changes in the skin and gastrointestinal tract lung and/or kidney in all nine patients Sclerodermatous parenchymal disease was severe in the lung in two patients and in the kidney in one (Case No 7) With the exception of the latter case the most striking abnormalities were present in the heart and in eight of the nine patients appeared to be the only cause of death

The hearts weighed from 250 to 475 Gm and three exceeded 350 Gm The extramural coronary arteries were widely patent in each patient In eight of the nine patients the intramural coronary arteries were morphologically normal on multiple histologic sections and by microangiogram in one (Fig 1) In one patient (Case No 2) focal thickening of approximately 10 per cent of the small vessels examined was observed and occasional thrombi were present within their lumens

The myocardium in all patients showed a similar lesion consisting of extensive focal fibrosis involving both right and left ventricle Focal areas of acute and subacute necrosis were also present in seven of the nine hearts and in each contraction bands were present within myocardial cells in focally necrotic zones of myocardium The areas of myocardial fibrosis and necrosis were not limited to the distribution of a particular extramural coronary artery but were randomly demonstrated throughout the myocardium from epicardium to endocardium and were present in both right and left ventricles In the 12 year old patient (Case No 1) who died during an episode of Raynaud s phenomenon contraction band necrosis was most striking and involved an estimated 30 per cent of myocardium (Fig 1) In none of the eight patients dying suddenly were other explanations for their sudden death evident at autopsy

Discussion

This report describes nine autopsied patients who had clinical histories characteristic of ischemic heart disease during life and myocardial necrosis and fibrosis at autopsy but widely patent coronary arteries Chest pain had been present in six of them during life and in three transient ischemic ST T wave changes were documented during episodes of pain Unexplained ventricular arrhythmias were also a feature of this group of patients Causes other than coronary disease were not available for most of these patients to account for their cardiovascular

Table 1 Patients studied

Case age/sex	General clinical findings	Cardiovascular findings	Autopsy findings
Sudden death			
1 12 F	Raynauds 1 yr fatigue leg cramps periorbital edema elevated CPK suspected functional illness Died in September	Normotensive after 3 days of severe Raynauds had unexpected cardiopulmonary arrest associated with *ST* elevation V_2 V_3 diagnosed as acute anterior MI	PSS lesions of skin esophagus kidney lungs Heart–normal IMCA EMCA 4+ focal CB necrosis subacute necrosis and 2+ focal fibrous scarring
2 38 M	Raynauds 1 yr fatigue darkening skin severe muscle weakness exertional dyspnea mild dysphagia mild restrictive lung disease weight loss Died in September	Normotensive mild CHF ECG–poor R wave progression suggestive of remote MI dull aching substernal chest pain 24 hours PTD unexplained complete heart block SD	Severe PSS lesions esophagus stomach colon mild pulmonary renal Heart–normal EMCA focal thickening and thrombi in IMCA severe (3+) focal fibrosis and CB necrosis (3+)
3 40 F	Tenosynovitis 4 yrs dermatitis dysphagia with abnormal esophageal duodenal and jejunal motility No pulmonary or renal dysfunction Died in July	Normotensive history of pericarditis recurrent anterior chest pain unknown etiology 6 weeks before death unexplained arrhythmias persisting over 10 days PTD including multifocal PVCs with bigeminy acute MI suspected SD	Mild PSS lesions esopahgus skin lung no renal disease Heart–normal EMCA IMCA extensive focal CB necrosis (4+) with inflammation focal fibrosis (2 3+)
4 40 F	Raynauds 3 yrs fatigue weight loss edema of hands and feet dysphagia diarrhea No renal or pulmonary dysfunction Died in July	Systemic hypertension intermittent precordial chest pain of unknown etiology dyspnea on exertion ECG–normal 3 days PTD had PAC PVC SD	Mild PSS lesions e ophagus skin kidneys no pulmonary lesions Heart–normal EMCA IMCA focal moderate (2 3+) fibro is and necrosis with contraction bands
5 50 M	Raynauds 2½ yrs digital ulcers increased skin pigmentation and tightening muscle weakness abnormal esophageal and small bowel motility no renal or pulmonary disease Died in June	Mild systemic hypertension (160/90) PVCs 9 months PTD unexplained CHF 2 months PTD improved on digitalis and diuretics SD	Severe PSS lesions esophagus mild lesions kin lung Heart–normal IMCA EMCA severe focal necrosis with contraction bands (4+) and focal fibrosis (3+)
6 70 F	Raynauds 20 yrs Skin thickening arthralgias restrictive lung disease (VC 75% predicted) recurrent bronchitis dysphagia Died in July	Normotensive CHF 2 years before death intermittent chest pain not relieved by nitroglycerin ECG–RBBB multifocal PVCs with bigeminy SD	Severe PSS lesions esophagu lung skin no renal disease Heart–normal EMCA IMCA moderate to severe focal scarring (3+) and focal necrosis (3+) with contraction bands

Abbreviations CB = contraction bands CHF = congestive heart failure CPK = creatinine phosphokinase ECG = electrocardiogram EMCA = extramural coronary arteries IMCA = intramural coronary arteries MI = myocardial infarction PAC = premature atrial contractions PSS = progressive systemic sclerosis PTD = prior to death PVC = premature ventricular contractions RBBB = right bundle branch block SD = sudden death VC = vital capacity yr = year
Grades of histologic injury 1+ trace 2+ mild 3+ moderate 4+ marked

dysfunction In six of the nine renal and pulmonary disease were mild or absent Only two patients had systemic hypertension and none had valvular heart disease

Sudden unexpected death occurred in eight of these nine patients (although in one patient sudden death was associated with worsening heart failure) and was presumed to be due to arrhythmias or myocardial infarction in all of them That sudden death was cardiac in origin was confirmed by autopsy Severe myocardial lesions were present, and no other cause of death was evident Perhaps most striking however was the finding of acute myocardial necrosis compatible with their clinical signs of ischemic heart disease but widely patent extramural coronary arteries and morphologically normal intramural coronary arteries

A clue to the pathophysiology of the seemingly ischemic heart disease with normal coronary arteries was present however in the type of myocardial damage Contraction band necrosis was present in seven patients Contraction band necrosis is a form of myocardial cell injury which

Table I Cont d

Case age/sex	General clinical findings	Cardiovascular findings	Autopsy findings
Angina pectoris with or without sudden death			
7 45 F	Raynauds 2 yrs arthralgias tightening of skin of hands face chest dysphagia no pulmonary disease acute renal failure and sepsis leading to death over 10 day period Died in July	Normotensive palpitations and substernal chest pain for 2 years positive Masters test congestive heart failure 1 month PTD	Mild to moderate PSS lesions esophagus small bowel lung severe renal disease Heart—normal EMCA IMCA severe focal scarring (4+) no necrosis fibrinous pericarditis
8 50 M	Raynauds 1 yr arthralgias mild dysphagia skin tightening over hands no pulmonary or renal problems. Died in February	Normotensive angina pectoris for 5 years with ST segment depression during pain CHF 1 year PTD ECG—left axis deviation PVC bigeminy rapidly progressive CHF with SD	Mild PSS lesions esophagus skin lung no renal disease Heart—normal EMCA IMCA marked focal scarring (3+) no necrosis
9 54 F	Raynauds 16 years dysphagia 6 years severe restrictive lung disease (V C 21% predicted) normal renal function marked increase in Raynauds over 3 weeks PTD leading to cold blue fingers by time of death purple with early trophic changes Died in January	Normotensive intermittent precordial chest pain 1 month PTD severe chest pain at rest associated with ST elevation V V with subsequent inversion of T waves V V for several days ECG RBBB PVC SD at home 10 days after hospital discharge	Moderate to severe PSS lesions esophagus, lung no renal disease Heart—normal EMCA IMCA Severe focal scarring (4+) and *focal acute necrosis (3+)* with contraction bands and acute inflammation

may be distinguished from the commonly recognized form of ischemic damage coagulation necrosis Coagulation necrosis can be produced experimentally by permanent occlusion of a coronary artery Contraction band necrosis less frequently seen and only recently recognized as a distinctive lesion differs morphologically from coagulation necrosis by the presence of dense eosinophilic transverse contraction bands[20-22] Experimental and clinical studies have led to the recognition of contraction band necrosis as a reperfusion lesion The lesion is frequently present in patients after cardiac surgery performed with cardiopulmonary bypass [23] and may be produced experimentally by *temporary* coronary artery occlusion followed by reperfusion That contraction band necrosis is a reperfusion lesion and was present in seven of our patients and in seven of the eight who died suddenly suggests that their myocardial damage was a consequence of transient nonperfusion

One possible explanation for transient nonperfusion of myocardium in these patients is recurrent spontaneous ventricular tachycardia or fibrillation For myocardial damage to result from an episode of spontaneous ventricular fibrillation the period of nonperfusion would have to be longer than several minutes however and none of these patients gave a history of syncope lapse of consciousness or previous cardiac arrest

Another possible explanation would be spasm or Raynaud s phenomenon of the coronary arteries Transient nonperfusion or Raynaud s phenomenon of the digits and kidneys[19] and possibly the lungs is a recognized feature of PSS and likely accounts for many of the morphologic changes observed in these organs It is similarly likely that the myocardial damage is due to a Raynaud s phenomenon of the intramyocardial arteries of the heart Intermittent vascular spasm at some level of the microcirculation would also account for the contraction band type of necrosis Such injury would be cumulative and would explain both the necrosis and fibrosis present in these patients and its presence throughout both right and left ventricle Coronary angiography in one patient with PSS myocardial disease has been reported [4] and in that patient the extramural coronary arteries were normal but there was unusually slow clearance of contrast material from the coronary vessels suggesting increased resistance of the capillary bed due to some abnormality of the

microcirculation Since we found no consistent morphologic abnormalities in the small coronary vessels of 52 patients (20) with PSS including eight of the nine described here, it is most likely that the abnormality is functional rather than structural

That epicardial coronary arterial spasm can last long enough to cause not only myocardial ischemia but also infarction has been demonstrated angiographically in patients with patent coronary arteries [5, 6] Engel and colleagues[26] recently described a patient with myocardial infarction resulting from angiographically documented spasm of the right coronary artery and otherwise normal coronary arteries who had a possible Raynaud s phenomenon of the hands and feet during episodes of chest pain

In our nine patients with PSS a Raynaud's phenomenon of the heart would explain angina pectoris, ventricular arrhythmias and sudden death Transient ischemic changes in electrocardiograms in three patients during angina and the preterminal electrocardiographic evidence of transmural ischemia in the 12 year old girl all in the setting of morphologically normal coronary arteries supports the notion of some type of intermittent spasm Two patients died suddenly after several days of severe persistent Raynaud's phenomenon of the fingers Contraction band necrosis was most prominent in both of their hearts Although the temporal relationship between Raynaud's phenomenon of the digits and a similar phenomenon in the lungs kidneys or heart is not necessary Cannon and associates [19] using Xe^{133} washout techniques and renal arteriography, demonstrated reductions in renal cortical blood flow in a few patients with PSS when Raynaud's phenomenon of the hands was induced by cold water immersion

Cannon and associates[19] also performed a seasonal analysis of deaths in their patients with PSS and showed that among 40 patients three fourths of all deaths caused by malignant hypertension and renal failure occurred in the fall and winter months They suggested that sudden transition from warm to cold climate may have been analogous to 'cold immersion A similar analysis of our patients with cardiac PSS failed to show such a striking seasonal relationship to mortality Half of our patients with sudden cardiac death died in the fall or winter months and this included the two patients dying during episodes of Raynaud s phenomenon The other half of the sudden death group, however, died in June or July and it was impossible to determine whether these patients were subject to sudden temperature changes such as those associated with exposure to air conditioning

There has been considerable interest in the mechanism of angina pectoris and myocardial infarction in the setting of normal coronary arteries by angiography It is likely that many processes may account for this condition, and proposed mechanisms have included coronary arterial embolism and lysis extramural arterial spasm, abnormalities and lactate metabolism and abnormalities of oxyhemoglobin dissociation [2, 10] Nonetheless evidence for these mechanisms is sparse, autopsy confirmation of the myocardial lesion and the coronary arterial patency infrequent and the existence of the condition as a single pathophysiologic entity is controversial These nine patients with PSS represent one of the largest autopsy series of angina pectoris, and/or myocardial infarction' with normal coronary arteries In them a pathophysiologic mechanism, episodic spasm of intramyocardial vessels, seems to be one explanation for their clinical and pathological features As such, the patients with PSS, and what may be a myocardial Raynaud's phenomenon, form a possible model for one form of angina or infarction with normal coronary arteries

Summary

The syndrome of angina pectoris or acute myocardial infarction without obstructive coronary artery disease has been the subject of much interest We studied nine autopsied patients with progressive systemic sclerosis and evidence of ischemic heart disease but morphologically normal coronary arteries Three patients had angina pectoris and three others chest pains of unknown etiology six had ventricular arrhythmias four had clinically suspected acute myocardial infarction and eight had sudden cardiac death At autopsy extensive focal myocardial necrosis was present in seven patients and myocardial scarring in all nine but all patients had widely patent intramural and extramural coronary arteries The finding of contraction band myocardial necrosis in seven of the eight patients who experienced sudden death suggests that the myocardial damage was a consequence of

reperfusion of focally nonperfused myocardium and thus due to a myocardial Raynaud s phenomenon Patients with PSS may provide a model of spasm of intramyocardial vessels causing angina pectoris or myocardial infarction with morphologically normal coronary arteries

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Effect of coronary collaterals on left ventricular function at rest and during stress

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During recent years there still exists controversy concerning the effectiveness of coronary collateral vessels in man as a compensatory mechanism for the loss of blood flow consequent to coronary obstruction.[1-11] In the dog heart rudimentary collateral vessels enlarge during gradual occlusion of a major coronary artery and perfuse the myocardium distal to complete occlusion to such an extent that only little or no myocardial damage results in this area provided the luminal narrowing was slow enough.[12-23] Pathologic and angiographic studies in man have also shown that severe coronary obstructions are not regularly associated with transmural myocardial infarction or scars if an adequate compensating collateral circulation exists.[11, 4, 5] Large differences in size and extent of collaterals can be shown by angiography and comparison of preoperative angiograms and intraoperative flow measurements indicate that radiographic appearance of coronary collateral circulation is related to the flow capacity of these vessels.[30, 33] Furthermore normal flow in the area distal to complete coronary occlusion could be measured by radioisotope studies in several patients in whom cinearteriography revealed an adequate retrograde filling of the occluded artery.[24, 34] Therefore the angiographic evaluation seems to be a reliable method to estimate collateral flow. The purpose of this study was to investigate the adequacy of coronary collaterals in the presence of complete coronary occlusion by measuring total and regional left ventricular contractile function at rest and during stress. Clinical data were reviewed to compare coronary morphology and subjective complaints.

Methods

A consecutive series of 169 patients having significant coronary artery disease (more than 75 per cent luminal obstruction of at least one major coronary artery) was studied. From this series all patients with complete occlusion of the proximal part of at least one of the three major coronary arteries were selected (87 patients). Additional coronary stenoses of less than 75 per cent luminal narrowing were present in a few patients and were not considered. Patients with atrial fibrillation, with valvular heart disease, with severe disease of the main stem of the left coronary artery, and patients with technically poor angiographies were excluded from the study.

Cardiac catheterization was performed without premedication in the fasting state. A biplane cineventriculogram (30 degree right anterior oblique position, 50 ml. Renografin, 36 frames per second using 35 mm. films and six inch image intensifiers) was followed by coronary arteriography in the right and left anterior oblique positions using the Judkins technique. A pacing test was performed in a subgroup of 12 of 87 patients with complete occlusion of the descending branch of the left coronary artery. Six of these patients showed good collaterals and six showed poor collaterals (as defined below) to the occluded vessel. For this purpose a bipolar pacing electrode was placed into the apex of the right ventricle (via

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Fig 1A and B *A* Well collateralized occlusion of the anterior descending branch of the left coronary artery Left coronary injection RAO projection early filling phase complete occlusion of the anterior descending branch (*arrow*) with retrograde filling over a large collateral vessel (*arrowhead*) originating from the patent marginal branch *B* Late filling phase uninterrupted filling of the distal segment and septal branches are seen

femoral vein) Thirty minutes after the last coronary arteriogram right ventricular pacing was started at a rate of 110 b p m and was gradually increased under left ventricular pressure registration to a rate of 180 b p m This rate was kept constant for one minute After stopping of pacing ventriculography was immediately repeated If pain occurred during this procedure nitroglycerin was given after ventriculography and pain was relieved in all cases where it was observed

The coronary occlusions of the anterior descending branch (LAD) the circumflex branch (LC) of the left coronary artery and the right coronary artery (RC) as well as the collateral circulation were analyzed from the cineangiograms and were tabulated

Radiographic criteria for the presence of collateral vessels were (a) retrograde filling of a major vessel after injection of contrast medium into another vessel or (b) filling of the distal segment of a proximal occluded major vessel after injection into the proximal stump of the same artery Collateralization was termed good if the distal segment of the occluded artery and its branches was visualized without interruption and if the average caliber of the distal segment measured greater than 1 0 mm after correction for the angiographic magnification When the distal segment was interrupted and/or the average caliber was only 1 0 mm or less collateral circulation was considered poor Each case was evaluated including measurement of the distal segment by two observers In cases which showed two or three vessel occlusions good collateralization was accepted if each vessel fulfilled the criteria for good collaterals This classification of collaterals resembles that used by several investigators [8, 14] but differs from that used by others [4] Examples of well collateralized occlusions are shown in Figs 1 and 2

Quantitative biplane ventriculography was performed using the area-length method [6, 12] For calculation of segmental wall motion and LV volumes ectopic and postectopic cycles were eliminated The ventriculograms of 17 normal patients without heart disease (average age 44 3 ± 3 5 years) served as controls Biplane ejection fraction was derived from the ratio of angiographic stroke volume to end diastolic volume times 100 per cent Segmental wall motion was quantitatively analyzed according to the technique of Herman and Gorlin [1] End diastolic and end systolic silhouettes were outlined from the 30 degree right anterior oblique projection The long axis (L) was drawn from the midaortic root to the apex and three equally spaced perpendiculars were constructed creating six hemiaxis from the long axis to the endocardial surface These axis

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During recent years there still exists controversy concerning the effectiveness of coronary collateral vessels in man as a compensatory mechanism for the loss of blood flow consequent to coronary obstruction [1-11] In the dog heart rudimentary collateral vessels enlarge during gradual occlusion of a major coronary artery and perfuse the myocardium distal to complete occlusion to such an extent that only little or no myocardial damage results in this area provided the luminal narrowing was slow enough [12-3] Pathologic and angiographic studies in man have also shown that severe coronary obstructions are not regularly associated with transmural myocardial infarction or scars if an adequate compensating collateral circulation exists [8, 11, 24] Large differences in size and extent of collaterals can be shown by angiography and comparison of preoperative angiograms and intraoperative flow measurements indicate that radiographic appearance of coronary collateral circulation is related to the flow capacity of these vessels [30, 31] Furthermore, normal flow in the area distal to complete coronary occlusion could be measured by radioisotope studies in several patients in whom cinearteriography revealed an adequate retrograde filling of the occluded artery [32, 33] Therefore the angiographic evaluation seems to be a reliable method to estimate collateral flow The purpose of this study was to investigate the adequacy of coronary collaterals in the presence of complete coronary occlusion by measuring total and regional left ventricular contractile function at rest and during stress Clinical data were reviewed to compare coronary morphology and subjective complaints

Methods

A consecutive series of 169 patients having significant coronary artery disease (more than 75 per cent luminal obstruction of at least one major coronary artery) was studied From this series all patients with complete occlusion of the proximal part of at least one of the three major coronary arteries were selected (87 patients) Additional coronary stenoses of less than 75 per cent luminal narrowing were present in a few patients and were not considered Patients with atrial fibrillation with valvular heart disease with severe disease of the main stem of the left coronary artery and patients with technically poor angiographies were excluded from the study

Cardiac catheterization was performed without premedication in the fasting state A biplane cineventriculogram (30 degree right anterior oblique position 50 ml Renografin 36 frames per second using 35 mm films and six inch image intensifiers) was followed by coronary arteriography in the right and left anterior oblique positions using the Judkins technique [35] A pacing test was performed in a subgroup of 12 of 87 patients with complete occlusion of the descending branch of the left coronary artery Six of these patients showed good collaterals and six showed poor collaterals (as defined below) to the occluded vessel For this purpose a bipolar pacing electrode was placed into the apex of the right ventricle (via

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occlusions (10 patients). Isolated LC and two and three vessel occlusions were rarely found (Table I). The ejection fraction was significantly higher in well collateralized LAD occlusion and RC occlusion as compared to poorly collateralized occlusions of the same subgroup ($p < 0.001$). Comparison with the average of normal individuals shows no significant difference ($p > 0.05$) of ejection fraction in patients with well collateralized occlusion of LAD and occlusion of RC. In contrast, poorly collateralized occlusions of LAD, RC, LAD + RC, and RC + LC showed significantly depressed ejection fractions (all $p < 0.001$). All other subgroups were too small for statistical comparisons.

The analysis of segmental wall motion is shown in Table II. In poorly collateralized LAD occlusion anterior wall motion (R_1 to R_3, L) was significantly lower than in well collateralized LAD occlusion ($p < 0.05$, respectively, < 0.01, $p < 0.001$). The same was found in RC occlusion for inferior wall motion (R_4 to R_6). Comparison of normally contracting ventricles to well collateralized occlusions reveals slight hypokinesia of R and L in well collateralized LAD occlusion and normal motion in well collateralized RC occlusion ($p > 0.05$). Severely reduced wall motion was found in poorly collateralized occlusions of the same areas ($p < 0.01$, respectively, $p < 0.001$).

Table III presents mean values of anterior wall motion at rest and after pacing. Pacing drastically reduced wall motion in well collateralized LAD occlusions if sets of paired observations are compared ($p < 0.05$, respectively, < 0.01). Poorly collateralized occlusions, however, showed severely depressed wall motion at rest and remained unchanged after stress ($p > 0.05$).

Table IV summarizes clinical data of two patient groups with comparable numbers and localizations of coronary occlusions separated by the presence or absence of good collaterals. Patients with good collaterals to the occluded vessels have more severe angina ($p < 0.001$) and more severe ST segment changes during exercise ($p < 0.01$) than patients with poor collaterals. Patients with poor collaterals have more severe dyspnea ($p < 0.01$) and more histories of previous infarctions if compared to patients with good collaterals ($p < 0.001$).

Discussion

A well-developed collateral circulation supplying the distal segment of a completely

Table I. Ejection fraction at rest in patients with coronary artery occlusions and different stages of collateralization

	Good collaterals		Poor collaterals		
Occluded vessel	Pat. No.	Ejection fraction (%)	Pat. No.	Ejection fraction	P values
LAD	9	59.6 ± 2.3†	22	41.4 ± 1.4	p < 0.001
LC	4	66.5 ± 3.7	4	51.0 ± 4.0	—
RC	11	67.8 ± 2.1†	10	51.0 ± 2.6	p < 0.001
LAD + RC	4	69.0 ± 3.3	4	29.0 ± 1.4	—
LAD + LC	3	47.7 ± 2.1	6	34.7 ± 3.4	—
RC + LC	3	57.7 ± 3.7	5	45.0 ± 2.6	—
LAD + RC + LC	1	4? 0	1	33.0	—
Normal coronary arteries	17	65.2 ± 1.9			

Abbreviations: LAD = anterior descending branch of the left coronary artery; LC = circumflex branch of the left coronary artery; RC = right coronary artery; Pat. No. = number of patients.
= $p < 0.001$ or † = $p > 0.05$ denotes significant differences if compared to the ejection fraction of patients with normal coronary arteries.
Mean values ± S.E.M.

occluded coronary artery preserves myocardial function partially. Preservation of myocardial function at rest was demonstrated by a normal ejection fraction, a nearly normal regional wall motion, and a low incidence of past myocardial infarctions. During stress the limited capacity of good collaterals was detected by a drastic fall of segmental wall motion after pacing and severe ST segment changes during treadmill exercise.

From dog experiments it is known that during gradual occlusion of a major coronary artery collaterals enlarge rather rapidly by an active growth process.[3] The degree to which collaterals can protect the myocardium depends on the time available for their development.[13,1] The higher the speed of the occlusion, the lower the chance for collaterals to compensate for it.[4] Quantification of the protective effect of collaterals on myocardial function during life requires comparison of patients with equal degree of coronary artery disease but with and without collaterals. Since the severity of coronary stenoses is difficult to measure angiographically, we investigated only patients with complete coronary artery occlusions. In addition, we believe that the effect of coronary collateral circulation can be evaluated in complete coronary artery occlusion

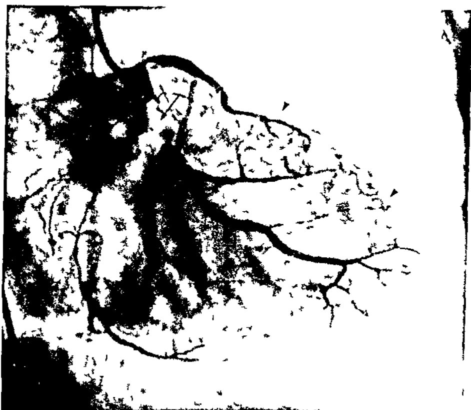


Fig 2 Well collateralized occlusion of the circumflex branch of the left coronary artery The occluded circumflex branch (*arrow*) shows complete retrograde filling from diagonal branches (*arrowhead*) In this case not a single large collateral vessel was found but an extensive collateral network was discovered instead In addition atrial collaterals to the right coronary artery are opacified

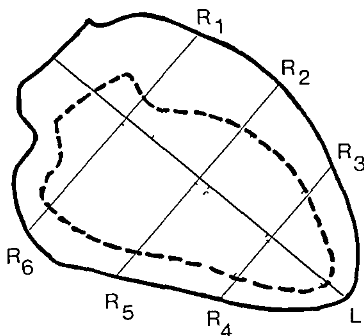


Fig 3 End diastolic and end systolic silhouettes are depicted with the system of hemiaxes

were drawn for each silhouette (Fig 3) The percentage shortening was calculated as diastolic minus systolic axis divided by diastolic axis times 100 per cent

Clinical data of patients with comparable numbers and localizations of coronary artery occlusions but different stages of collateralization were reviewed from 87 investigated patients to get two groups with comparable severity of coronary artery disease twenty patients had good and 27 had poor collaterals The history of angina pectoris and dyspnea was graded according to the NYHA Any history of previous myocardial infarction was noted based on clinical electro graphic and enzymatic data A treadmill exercise test was performed according to Kasser and Bruce[19] with continuous ECG monitoring The ST segment changes after submaximal exercise were measured and averaged over at least 10 beats

Results

Well collateralized occlusions were found in 35 patients poorly or not collateralized occlusions were found in 52 patients

Table I presents the average values of biplane ejection fraction at rest and the distribution into seven subgroups with various combinations of complete coronary occlusions separated by the degree of collateralization Well collateralized LAD occlusions were found less frequently (nine patients) than poorly collateralized LAD occlu sions (22 patients) Well collateralized RC occlu sions (11 patients) were found with equal frequency compared to poorly collateralized RC

between our results and those of Helfant and *colleagues*[2] Lavine and co workers[5] and Caroll and associates[6] These studies investigated patients with stenoses greater than 75 per cent Helfant and colleagues and Lavine and co workers[5] subdivided collaterals into present or absent Caroll and associates differentiated four collateral classes (no poor fair good) The groups with collaterals showed an equal * or increased number of abnormal ventriculograms as compared to the group without collaterals The conclusion was that collaterals do not protect from the development of ventricular asynergy This disagreement is probably due to the different patient populations studied (stenoses of more *than 75 per cent* * *or complete occlusion in our* study) and to the different gradations used for collaterals

Our clinical data revealed a high incidence of severe angina and marked ST segment changes during exercise in patients with good collateralization In addition pacing stress induced a marked reduction of wall motion indicative of acute myocardial ischemia in the e patients These findings are in accordance with the experience of others who reported no protective effect of coronary collaterals against acute myocardial ischemia as measured by treadmill stress test This implies that the area perfused by good collaterals mainly consisting of viable myocardium becomes ischemic since collaterals are not able to increase their flow capacity proportional to the increased oxygen demands

Summary

The influence of coronary collateral vessels on resting left ventricular function was investigated in 87 consecutive patients with complete coronary artery occlusion of at least one of the three major coronary vessels The morphology of coronary and collateral circulation was evaluated by coronary arteriography Left ventricular function was assessed by biplane ejection fraction and segmental wall motion was evaluated by *hemi* axes shortening Collaterals to occluded arteries were graded as good or poor according to the caliber of the distal vessel segment Patients were divided into those with good collaterals (n = 35) and those with poor or absent collaterals (n = 52) furthermore these two *groups* were subdivided according to the location of coronary artery occlusion Collateralized single vessel occlusions were found more frequently than collateralized multiple vessel occlusions Ejection *fraction and segmental wall motion was* significantly better in well collateralized occlusions than in poorly collateralized occlusions of LAD or RC and was normal or depressed only slightly if compared to 17 patients without heart disease In contrast total and regional myocardial function was severely depressed in poorly collateralized LAD or RC occlusion Ventriculography after rapid ventricular pacing was performed in 12 of 87 patients with well collateralized *or poorly collat*eralized LAD occlusion to evaluate to what extent coronary *collaterals protect anterior wall* motion during increased oxygen demand Pacing induced a drastic fall of anterior wall motion in well collateralized segments whereas no change was found in poorly collateralized segments Reviewing clinical data of two patient groups with comparable numbers and locations of occlusions revealed in the well collateralized group more severe angina ($p < 0.001$) and ST segment *changes* during exercise ($p < 0.01$) than in the poorly collateralized group The latter showed more severe dyspnoe ($p < 0.01$) *and more* histories of previous infarctions ($p < 0.001$) We conclude that well developed collateral vessels to a complete *occluded* artery prevent severe asynergy at rest but not during stress

Table IV Clinical data of patients with equal numbers and localizations of coronary artery occlusions and different stages of collateralization

	Good collaterals	*Poor collaterals*	*P values*
Anginal pain (NYHA Class)	3 4 ± 0 2†	1 3 ± 0 3	<0 001
Exercise test (ST changes in mV)	0 30 ± 0 04	0 13 ± 0 03	<0 01
Dyspnea (NYHA Class)	0 6 ± 0 [illegible]	1 9 ± 0 3	<0 01
History of previous infarction	[illegible]0%	89%	<0 001

†Mean values ± S E M

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Table II *Segmental wall motion at rest in patients with coronary artery occlusion and different stages of collateralization*

		Shortening of hemiaxes						
		R_1	R_2	R_3	R	R_5	R	L
LAD Occlusion	Good collaterals	47 4 ± 3 8†	33 0 ± 2 3	36 1 ± 2 3	46 3 ± 5 9	39 8 ± 3 7	20 8 ± 4 0	12 7 ± 1 9
	Poor collaterals	26 4 ± 4 3 *	11 9 ± 3 1 *	9 8 ± 3 3***	28 5 ± 5 8	36 4 ± 2 9	26 8 ± 1 7	8 3 ± 1 0
P values		<0 01	<0 001	<0 001	n s	n s	n s	<0 05
RC Occlusion	Good collaterals	55 7 ± 4 1	47 0 ± 4 8	45 7 ± 3 9	35 9 ± 3 6	30 3 ± 3 6	21 9 ± 2 8	20 6 ± 1 3
	Poor collaterals	43 9 ± 5 9	36 2 ± 5 4	40 1 ± 5 3	10 7 ± 4 8***	5 9 ± 3 0*	13 1 ± 2 9 *	16 4 ± 1 6
P values		n s	n s	n.s	<0 001	<0 001	<0 05	n s
Normal coronary arteries		52 6 ± 5 7	47 0 ± 4 1	42 1 ± 2 5	34 0 ± 3 2	32 3 ± 3 1	27 0 ± 2 8	19 4 ± 3 4

Abbreviations LAD = anterior descending branch of the left coronary artery RC = right coronary artery
* = p < 0 05 ** = p < 0 01 *** = p < 0 001 denotes significant differences between the groups with occluded vessels and patients with normal coronary arteries
†Mean values ± S E M

Table III *Anterior wall motion at rest and after pacing in patients with LAD occlusion and different stages of collateralization*

	Shortening of hemiaxes (%)							
	Good collaterals				Poor collaterals			
	R	R	R_3	L	R	R	R	L
Rest	56 2 ± 3 9†	36 0 ± 2 5	32 0 ± 4 1	9 8 ± 2 6	26 7 ± 9 1	10 0 ± 4 0	4 0 ± 2 7	6 2 ± 0 7
Pacing	25 8 ± 6 5	15 7 ± 3 5	10 3 ± 6 1	5 8 ± 1 1	20 2 ± 5 0	9 5 ± 3 6	3 0 ± 2 4	5 8 ± 1 4
P values	<0 01	<0 01	<0 05	n.s	n s	n s	n s	n.s

†Mean values ± S E M

only, since any additional flow through coronary stenoses may contribute to preservation of myocardial function In the dog heart it could be demonstrated that maximal collateral flow to the perfusion beyond a stenosis is not achieved before the vessel is completely occluded [20]

Patients with well collateralized occlusions showed higher ejection fractions better regional wall motion and a smaller percentage of previous myocardial infarctions in contrast to patients with poor collaterals The latter patients had severely depressed myocardial function Their dysfunction is caused by severe loss of wall motion in the area previously supplied by the occluded artery The loss of wall motion associated with a high incidence of previous infarctions suggests that asynergy in these patients is a result of myocardial fibrosis This is confirmed by results of Starr and associates[11] who found in 35 of 36 patients with severe left ventricular segmental contraction abnormalities significant myocardial fibrosis in the corresponding left ventricular wall at autopsy

Our results are in agreement with the findings of others Levin[10] reported normal contractility at rest in 43 per cent hypokinesia in 52 per cent and akinesia in 5 per cent of 86 completely occluded adequately collateralized arteries while occlusions with inadequate collaterals showed normal contractility in only 11 per cent hypokinesia in 16 per cent and akinesia in 73 per cent Gensini and da Costa[8] described five patients with completely obstructed arteries and collaterals with normal resting electrocardiograms while all patients without collaterals had abnormal electrocardiograms There is considerable disagreement

between our results and those of Helfant and colleagues Lavine and co workers[1] and Caroll and associates[6] These studies investigated patients with stenoses greater than 75 per cent Helfant and colleagues and Lavine and co workers subdivided collaterals into present or absent Caroll and associates[6] differentiated four collateral classes (no poor fair good) The groups with collaterals showed an equal [6] or increased number of abnormal ventriculograms as compared to the group without collaterals The conclusion was that collaterals do not protect from the development of ventricular asynergy This disagreement is probably due to the different patient populations studied (stenoses of more than 75 per cent [6] or complete occlusion in our study) and to the different gradations used for collaterals

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Dyspnea (NYHA Class)	0 6 ± 0 2	1 9 ± 0 3	<0 01
History of previous infarction	?0%	80%	<0 001

†Mean values ± S E M

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Echocardiography in chronic alcoholics following prolonged periods of abstinence

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Left ventricular studies utilizing M mode echocardiography have proved valuable in *the noninvasive* assessment of left ventricular function [1-6] Furthermore recent investigation supports echocardiography as a sensitive technique *for detecting* small changes in left ventricular end diastolic volumes [7] Systolic time intervals derived conventionally from simultaneous *recordings of the* carotid pulse and the ECG have also been useful in the evaluation of left ventricular function [8, 9] These intervals can also be conveniently and accurately derived from echocardiographic recordings of the aortic root [10-12] McDonald and Hobson[13] have concluded that the combined information derived from the measurement of left ventricular dimensions and systolic time intervals was superior to either method used alone

Alcohol has been incriminated as an etiologic factor in the development of left ventricular failure by a direct cardiotoxic effect [14-18] Abnormalities of left ventricular function have been documented utilizing both invasive and noninvasive methods in chronic alcoholics [19-24] Transient depression of left ventricular function has also been noted *in normal volunteers immediately* following alcohol consumption [25-27]

Although alcohol is known to freely pass the *placental barrier,*[28] *no analysis of left ventricular* function has been made in children born of alcoholic mothers

We have elected to utilize echocardiographic techniques of left ventricular function in studying chronic asymptomatic alcoholics following a long *period of abstinence and a small group of asymp*tomatic children born of chronic alcoholic mothers who were actively drinking during their *pregnancy*

Materials and methods

Twenty six *adult volunteers* (19 *men* and 7 women mean age 45 years range 25 to 62 years) form the basis of this study The duration of active alcoholism in these individuals averaged 18 3 years (range 4 to 40 years) Their mean duration of abstinence from alcohol was 3 1 years (range 3 months to 17 years) (Table I) Additionally seven asymptomatic children born of four alcoholic mothers belonging to the above group who were drinking throughout their pregnancy was also included in the study Their average age *was 14 1 years (range 4 to 19 years) A comparison* group of age matched normal individuals (13 adults and 8 children) was also studied

A detailed medical history physical examination 12 lead ECG and an echocardiographic examination performed in the standard manner were obtained in all

All echo examinations were performed with a *commercially available Picker echograph and a* 2 25 m Hz transducer Continuous records were obtained at 125 mm /sec on 35 mm film using a *slave oscilloscope and a* Fairchild record camera

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The following echo parameters were studied (Figs 1 and 2)

1 *Percentage of left ventricular dimension shortening (per cent ΔS)* [2]

$$\% \Delta S = \frac{D - D}{D} \times 100$$

The left ventricular diastolic dimension (D_D) measured in mm was the perpendicular distance between the left septal and left ventricular posterior wall endocardial surfaces measured at the R wave peak of a simultaneously recorded ECG The left ventricular systolic dimension (D_S) was measured in mm as the shortest perpendicular distance between the endocardial surfaces of the left side of the ventricular septum and the left ventricular posterior wall during systole

2 *Left ventricular ejection fraction (EF)*

$$EF = \frac{D - D}{D} \times 100$$

3 *Mean velocity of circumferential fiber shortening (mean V_{CF})*

$$\text{mean } V = \frac{D_i - D}{D_D \times dt}$$

This was expressed in circumferences/second Left ventricular ejection time (dt) measured in msec was the period from the onset of systolic anterior motion of the left ventricular posterior wall to its maximal anterior excursion

4 *Systolic velocities of the ventricular septum and left ventricular posterior wall* These were measured in mm /sec as the maximal slope of the endocardial surfaces of the ventricular septum and left ventricular posterior wall respectively during systole

5 *Excursion of the ventricular septum and left ventricular posterior wall* These were measured in mm as the maximum perpendicular distance from the diastolic endocardial surface of the ventricular septum and left ventricular posterior wall to the level of their maximal systolic excursions

6 *The systolic time interval ratio (PEP/LVET)* Pre ejection period (PEP) measured in msec was the interval from the onset of the Q wave of the ECG to the point of opening of the aortic valve on the echogram Left ventricular ejection time (LVET) measured in msec was the interval from the opening to the closing of the aortic valve on the echogram

7 *Ventricular septal thickness* [30] This was measured in mm as the distance between the right and left endocardial surfaces of the ventricular septum at the time of the R wave peak from a simultaneously recorded ECG

8 *Left ventricular posterior wall thickness* [30] This was measured in mm as the distance from left ventricular endocardial to epicardial surfaces at the time of the R wave peak from a simultaneously recorded ECG

9 *Mitral valve EF slope* [31] This was measured as the maximal slope of the tangent between the mitral valve E to F points in diastole and was expressed in *mm /sec*

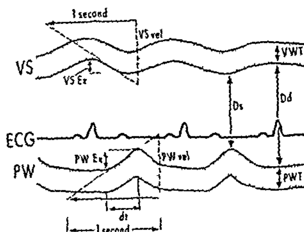


Fig 1 Diagram showing relationship between ECG tracing excursion of ventricular septum and LV posterior wall and other phenomena *VS* = ventricular septum *VS Ex* = maximal excursion of ventricular septum *VS vel* = maximal systolic velocity of the ventricular septum *PW* = left ventricular posterior wall *PW Ex* = maximal excursion of the left ventricular posterior wall *PW vel* = maximal systolic velocity of the left ventricular posterior wall *PWT* = posterior wall thickness *VWT* = ventricular septal thickness *Dd* = end-diastolic dimension *Ds* = end systolic dimension *dt* = duration of left ventricular systole

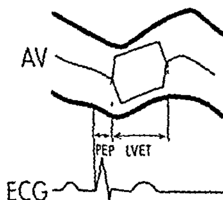


Fig 2 Diagram showing relationship between ECG *tracing* and pre-ejection period and left ventricular *ejection time in* the aortic valve *AV* = aortic valve *PEP* = pre-ejection period *LVET* = left ventricular ejection time

Table I Duration of abstinence

Period	Number of patients
3 months to 1 year	9
2 to 5 years	7
6 to 10 years	4
Over 10 years	6

Table II Echocardiographic values in adults

	Normal (13 subjects)		Alcoholic (26 subjects)	
	Mean	Range	Mean	Range
PW Ex (mm)	12 8	8 22	13 6	8 20
Vel (mm /sec)	45 0	30-100	50 6	30 80
Thick (mm)	7 2	6 10	7 8	7 9
VS Ex (mm)	8 6	5 13	7 7	5 12
Vel (mm /sec)	33 9	20 50	32 9	25 50
Thick (mm)	9 1	7 11	9 4	7 14
ΔS (%)	39	30 59	38	21 54
EF (%)	78	66 97	75	42 90
V_{cf} (circumferences /sec)	1 18	0 80 1 58	1 13	0 40 1 67
PEP/LVET	0 29	0 23 0 36	0 31	0 23 0 36
EF slope (mm / sec)	102 0	70 130	106 0	75 140

Includes only 20 subjects

Abbreviations PW = left ventricular posterior wall Ex = maximal excursion Vel = maximal systolic velocity Thick = thickness VS = ventricular septum %ΔS = % shortening of left ventricular dimension EF = ejection fraction V_{cf} = mean velocity of circumferential fiber shortening PEP/LVET = pre ejection period/left ventricular ejection EF slope = maximal mitral valve EF slope

Table III Echocardiographic values in children

	Normal (8 subjects)		Children of alcoholic mothers (7 subjects)	
	Mean	Range	Mean	Range
PW Ex (mm)	12 6	7 17	10 3	8 13
Vel (mm /sec)	50 0	35 75	41 4	35 50
Thick (mm)	7 5	6-8	7 6	7 8
VS Ex (mm)	6 7	5 9	6 9	5 10
Vel (mm /sec)	33 6	20-50	35 0	25 50
Thick (mm)	9 0	7 11	9 2	7 11
ΔS (%)	42	30-48	37	30-45
EF (%)	80	68 86	74	66 83
V_{cf} (cir /sec)	1 21	0 82 1 65	1 14	0 86 1 5
PEP/LVET	0 28	0 25 0 33	0 29	0 27 0 32
EF slope (mm /sec)	108 0	85 130	110 0	100 125

Includes only two subjects

For abbreviations please refer to Table II

Results

History physical exam and ECG None of the 26 alcoholics had evidence on physical examination of cardiac abnormality Two had mild chronic obstructive pulmonary disease One individual had a myocardial infarction approximately one year ago but no residual ECG abnormalities None of the others had ECG abnormalities apart from one adult individual who had congenital complete heart block

The seven children had no evidence of cardiac abnormality by history, physical examination or ECG

Echocardiography These results are summarized in Tables II and III

Adequate echograms of the left ventricular cavity (Fig 3) were obtained in all adult alcoholics and children of alcoholic mothers The parameters of left ventricular function were found to be normal in all except one adult alcoholic when compared to age matched controls This individual was a 41 year old white male with a 19 year history of alcoholism and a one year period of abstinence He had no history of cardiac disease, no cardiovascular symptoms and his physical examination and ECG were normal His per cent ΔS (21 per cent) EF (42 per cent) and mean V_{cf} (0 40 circumferences/sec) were depressed His PEP/LVET ratio could not be measured since adequate recordings of the aortic valve were not obtained One additional adult alcoholic had a slightly thickened ventricular septum (14 mm)

PEP/LVET ratios were obtained in 20 of 26 adult alcoholics and two of the seven children (Figs 2 and 4) None had an abnormal value

Discussion

Alcohol has a direct toxic effect on cardiac musculature [17] Mitochondrial damage with decreased mitochondrial oxidative enzymes results in diminished energy production and decreased contractility [14] Changes in sarcoplasmic reticulum appear responsible for impaired excitation-contraction coupling with decreased calcium delivery to the contractile apparatus [17] Additionally acetaldehyde the principal metabolite of ethanol causes myocardial release of norepinephrine and this catecholamine depletion may contribute to decreased left ventricular contractility [18] Although the associated nutritional deficiencies of thiamine and nicotinic acid may occasionally play a role in the cardiovascular disease



Fig 3 Normal echocardiogram of a left ventricular dimension in a chronic alcoholic patient following a long period of abstinence VS = ventricular septum PW = left ventricular posterior wall ECG = electrocardiogram

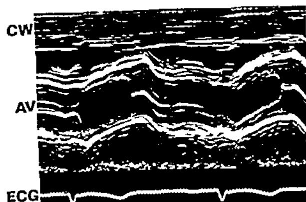


Fig 4 Normal echocardiogram of the aortic root in a chronic alcoholic patient following a long period of abstinence AV = aortic valve CW = chest wall ECG = electrocardiogram

of chronic alcoholism [3] [23] the hyperkinetic left ventricular abnormality produced by these states differs greatly from the hypokinetic low cardiac output syndrome associated with the cardiac failure of the chronic alcoholic [7]

Clinical experiments using normal volunteers and animals have shown transient depression of left ventricular function following acute ingestion of alcohol This has been demonstrated by cardiac catheterization echocardiography and systolic time intervals measured in the conventional manner [7] Cardiomyopathy with clinically obvious cardiac decompensation has been documented in chronic alcoholics who had no known evidence for underlying heart disease [5] [7]

Depression of left ventricular function has also been noted in chronic alcoholics who have had no clinical evidence of cardiac dysfunction [21] Regan and colleagues studied a group of chronic alcoholic subjects with cardiac catheterization using angiotensin infusion to increase left ventricular afterload Significant abnormal elevation of left ventricular diastolic pressure as well as decreased left ventricular contractility were noted

In two separate investigations Spodick and co workers[2] and Wu and associates studied chronic alcoholics who had no cardiac symptoms and found abnormal systolic time intervals indicating left ventricular dysfunction in both groups Matthews and colleagues utilized echocardiography to evaluate 26 asymptomatic alcoholics and found 81 per cent with thickened left ventricular posterior walls and 35 per cent with decreased mitral EF slopes

All except one in our study had normal echocardiographic indices of left ventricular function while none had evidence by history physical examination or ECG of ventricular dysfunction The longer period of abstinence of our alcoholic population may account for this difference The studies of Regan and colleagues[19] were performed after approximately 3 weeks hospitalization and the investigation of Wu and associates[23] was conducted on alcoholics with mean periods of abstinence of only 12 days The alcoholics in the study by Spodick and co workers[2] were examined 2 to 3 days after their last alcohol ingestion while the alcoholic group of Matthews and colleagues[4] were studied after only a two week minimum interval of abstinence On the other hand all our alcoholics had not ingested alcohol for a significantly longer period (mean duration 3 1 years) (Table I)

The period of active alcoholism in our group appears comparable in duration to that of Regan and associates[1] (at least 10 years) Matthews and co workers [4] (at least 6 years) and Wu and colleagues [3] (average duration of 15 years) while no information regarding this factor is found in the study by Spodick and collaborators [2]

In view of the left ventricular dysfunction documented by others in chronic asymptomatic alcoholics within a short period of abstinence it is possible that our population had abnormal left ventricular function when they were actively drinking or earlier in their period of abstinence and later reverted to normal However none of our subjects were studied while actively drinking or earlier in their period of abstinence and no data are available regarding the functional status of their left ventricle during that time No assumptions can thus be made regarding the presence of left ventricular dysfunction in our subjects in the early stages of rehabilitation

despite the accounts in the literature Although no longitudinal objective studies have so far been performed in symptomatic alcoholics with cardiac dysfunction, clinically demonstrable improvement of their left ventricular failure has been reported in significant numbers following complete cessation of alcohol consumption [15, 19, 34] Additionally, reversal of alcoholic cardiomyopathy following abstention from alcohol has been documented by cardiac catheterization and angiography in a single instance [35]

It has been suggested that alcohol might damage the developing fetus, although direct proof is lacking [6] Alcohol freely passes the placental barrier and high blood levels have been found in newborn infants comparable to those of their mothers [28] Alcohol withdrawal syndrome as well as central nervous system depression have been reported in the newborn [37, 39]

In the present investigation only a small number of children with prolonged exposure to alcohol in utero were studied However the finding of normal left ventricular parameters in all of them would suggest that alcohol does not affect left ventricular function when these children are assessed by echocardiography after a long interval following exposure to alcohol

In conclusion, our study demonstrates no clinical or echocardiographic evidence of left ventricular dysfunction in asymptomatic chronic alcoholic adults or in children born of alcoholic mothers when studied following a long period after alcohol exposure Although it might prove difficult, there is a need for a prospective longitudinal study of chronic alcoholics while they are drinking and serially during the course of their rehabilitation to objectively determine the incidence of left ventricular dysfunction induced by alcohol and its potential reversibility following alcohol withdrawal

Summary

Left ventricular function was analyzed using standard echocardiographic techniques in 26 chronic asymptomatic alcoholics without clinical evidence of cardiovascular disease All were studied following a long period of abstinence (mean 3 1 years range 3 months to 17 years) Seven asymptomatic children (mean age 14 1 years range 4 to 19 years) whose mothers had been actively drinking throughout their pregnancies were also studied The calculated fractional shortening of the left ventricle (per cent ΔS) ejection fraction, mean velocity of circumferential fiber shortening (mean V_{cf}) excursions and maximal systolic velocities of the ventricular septum and left ventricular posterior wall, pre ejection period/left ventricular ejection time ratios mitral valve EF slopes and thicknesses of the left ventricular posterior wall and ventricular septum were obtained in all Normal left ventricular function was found in all but one adult alcoholic In this patient, the per cent ΔS, ejection fraction, and mean V_{cf} were reduced One additional adult alcoholic had a minimally thickened ventricular septum Our results differ from other studies which have shown significant left ventricular dysfunction in asymptomatic chronic alcoholics A possible explanation is the much longer period of abstinence of our chronic alcoholics at the time of their examinations It also appears that left ventricular function in children born of alcoholic mothers is not affected when assessed after the long interval following prolonged exposure to alcohol in utero

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Cardiac abnormalities in cachectic patients before and during nutritional repletion

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Several investigators have studied the effects of protein-calorie undernutrition (PCU) on cardiac structure, size, and function in both man and the experimental animal [1-7] Although Voit[1] described a normal cardiac weight in protein deficient cats at autopsy and concluded that the heart is spared during starvation,' subsequent studies have indicated that cardiac atrophy occurs during inanition Smythe and colleagues and Wharton and associates[3] observed subnormal cardiac weight in approximately 50 per cent of severely undernourished South African and Ugandan children studied at autopsy Chauhan and co workers[4] reported that 3 months of a protein deficient diet in the monkey caused a 15 per cent reduction in cardiac weight and microscopic evidence of cardiac atrophy and fibrosis [4] These animals however experienced a 20 per cent loss in body weight and the microscopic changes in skeletal muscle were more advanced than those in the myocardium Wharton and colleagues[3] described a diminished radiographic cardiac size in Ugandan kwashiorkor patients and concluded that this was proportional to their loss in body weight These investigators reported microscopic cardiac lesions (e g vacuolation of myofibrils and fibrosis) at autopsy Similar pathology however, was present in control patients and Wharton and associates concluded that these lesions were not specific for kwashiorkor Keys and colleagues[5] observed that in human volunteers exposed to inadequate protein-calorie intake for 6 months the radiographic cardiac size diminished but the decrease in heart volume was only 70 per cent that observed in total body weight

With regard to cardiac function Edozien and Rahim Khan[6] and Wharton and co workers[3] described normal clinical cardiac status in children with kwashiorkor prior to nutritional therapy Keys and colleagues[5] and Alleyne [7] on the other hand reported reduced cardiac output in both undernourished adults and in children with kwashiorkor

While different impressions of cardiac structure and function in the cachectic state have been reported most investigators have agreed that when such patients are repleted evidence of circulatory failure frequently occurs Wharton and colleagues [3] Keys and co workers[5] and Edozien and Rahim Khan described a progressive increase in radiographic heart size during repletion that was proportionately greater than the gain in body weight An increase in electrocardiographic (ECG) voltage (Wharton and associates[3]) suggested a parallel enlargement in left ventricular mass Alleyne[7] and Keys and colleagues[5] also observed progressive augmentation in stroke volume and cardiac output during repletion In 20 to 30 per cent of Edozien and

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Table I Clinical history and nutrition data base

Patient	Age	Sex	Primary diagnosis	Anthropometric indices				Subnormal laboratory values
				% BW	% 24 hr cr/ht	% TSF	% MAMC	
HC	52	F	Psychogenic anorexia	64	54	35	74	SCa
AB	56	F	Multiple complications from intestinal surgery	65	34	37	56	SALB HCT RBC FOLATE SCa SZn
SF	35	F	Crohn s disease	85	63	42	[illegible]5	SALB HCT SCAR SCa SMg
HG	[illegible]6	M	Chronic lymphocytic leukemia	60	35	2[illegible]	65	SZn
SC	32	M	Cirrhosis	E†	38	60	73	SALB HCT SCAR SMg SCa
BH	48	F	Peptic ulcer disease	55	63	30	65	SALB HCT
WW	36	F	Psychogenic anorexia	60	32	53	58	SALB HCT RBC FOLATE
PS	56	F	Whipple procedure for suspected carcinoma of the pancreas	E	5[illegible]	24	72	SALB HCT SCAR
JK	68	M	Cancer of pancreas	E	29	30	[illegible]0	SALB HCT
SCR	34	F	Cancer of colon	[illegible]6	55	29	72	SALB HCT RBC FOLATE SCa

24 hr urine creatinine-to-height ratio is an index of lean body mass.
†E = edema weight therefore an unreliable index of nutritional state

Rahim Khan s cases signs of congestive heart failure occurred during the first 3 weeks of nutritional repletion (early recovery syndrome) Smythe and co workers and Keys and colleagues also noted cardiac dysfunction (e g an enlarged cardiothoracic ratio and a smaller stroke volume and cardiac output compared to pre starvation values) during recovery from protein deprivation in both children and adults

Three recent developments in nutrition and cardiology have led us to re examine in the present study cardiac size and function in cachectic patients before and during nutritional repletion (1) PCU is now common among hospital patients as indicated by a 30 to 40 per cent prevalence in recent surveys of two hospitals in the United States (2) effective methods for achieving rapid repletion of the cachectic patient by either the central intravenous peripheral intravenous or enteral route have now been developed and are in common use and (3) echocardiography is now available as an accurate non invasive method for quantitatively describing the anatomic dimensions and functional performance of the heart In phase A of the present study we utilized echocardiography and other non invasive techniques to characterize cardiac size and function in a group of 10 hospitalized patients with severe PCU In phase B five of these patients were repleted by intravenous or enteral hyperalimentation for a period of 3 to 6 weeks while we continued to monitor clinical status cardiac size and cardiac function

Methods

Subjects During July to December 1975 12 patients were referred to the Division of Nutrition at Emory University Hospital because of severe PCU as evidenced by these criteria loss of ≥ 25 per cent of body weight (BW) during past 2 years non edematous BW ≤ 85 per cent of ideal midarm muscle circumference (MAMC) and triceps skinfold (TSF) both ≤ 75 per cent of standard and 24 hour urine creatinine to height ratio (24 hr cr /ht) ≤ 75 percent of standard [11] Two patients had a history of heart disease preceding the present wasting illness and were excluded from this study the remaining 10 form the population for phase A A clinical description of these patients and selected results that describe their nutritional status are presented in Table I

Cardiac abnormalities in cachectic patients before and during nutritional repletion

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Several investigators have studied the effects of protein-calorie *undernutrition (PCU) on* cardiac structure, size and function in both man and the experimental animal [1-7] Although Voit[1] described a normal cardiac weight in protein deficient cats at autopsy and concluded that 'the heart is spared during starvation, *subsequent studies* have indicated that cardiac atrophy occurs during inanition Smythe and colleagues and *Wharton* and associates[3] observed subnormal cardiac weight in approximately 50 per cent of severely undernourished South African and Ugandan children studied at autopsy Chauhan and co workers[4] *reported that 3 months of a protein deficient* diet in the monkey caused a 15 per cent reduction in cardiac weight and microscopic evidence of cardiac atrophy and fibrosis[4] These animals however experienced a 20 per cent loss in body weight and the microscopic changes in skeletal muscle were more advanced than those in the *myocardium Wharton and colleagues*[3] described a diminished radiographic cardiac size in Ugandan kwashiorkor patients and concluded that this was proportional to their loss in body weight These investigators reported microscopic cardiac lesions (e g, vacuolation of myofibrils and fibrosis) at autopsy Similar pathology, however, was present in control patients and Wharton and associates concluded that these lesions were not specific for kwashiorkor Keys and colleagues[5] observed that in human volunteers exposed to *inadequate protein-calorie intake for 6 months* the radiographic cardiac size diminished but the decrease in heart volume was only 70 per cent that observed in total body weight

With regard to cardiac function, Edozien and *Rahim Khan*[6] *and Wharton and* co workers[3] described normal clinical cardiac status in *children with kwashiorkor prior to nutritional* therapy Keys and colleagues[5] and Alleyne, on the other hand reported reduced cardiac output in both undernourished adults and in children with kwashiorkor

While different impressions of cardiac structure and function in the cachectic state have been *reported most investigators have agreed* that when such patients are repleted evidence of circulatory failure frequently occurs Wharton and colleagues Keys and co workers[5] and Edozien and Rahim Khan described a progressive increase in radiographic heart size during repletion that was proportionately greater than *the gain in body weight An increase in* electrocardiographic (ECG) voltage (Wharton and associates[3]) *suggested a parallel enlargement in left* ventricular mass Alleyne[7] and Keys and colleagues[5] also observed progressive augmentation in stroke volume and cardiac output during repletion In 20 to 30 per cent of Edozien and

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Table II Hyperalimentation protocols for five malnourished patients during phase B

Patient	Type of HA	Duration of HA (days)	Daily intake: Calories (kcal)	Carbohydrate (Gm)	Fat (Gm)	Protein (Gm)
S C	P_{800} + oral feedings	20	29?0	363	122	92
B.H	C_{800}	30	3468	867	0	135
W W	Isocal via NGT	30	3000	375	126	75
P.S	Vivonex HN via NGT and Intralipid + P_{800}	35	3471	487	120	109
S C R	Isocal via NGT	30	3628	450	151	117

Intakes of Na K Cl Mg P Ca and Mn were one to three times the recommended daily allowance (RDA)
All abbreviations are defined under Methods section

Table III Radiographic and echocardiographic cardiac dimensions in malnourished patients (Phase A)

	Chest x ray		Echocardiogram								
Patient	RHV (c c)	RHV/BW (c c /Kg)	EdV (c c)	EdV/BW (c c /Kg)	EsV (c c)	EsV/BW (c c /Kg)	LVWTd (mm)	LVWTs (mm)	IVSd (mm)	LV mass (Gm)	LV mass/BW (Gm /Kg)
H.C	443	11 5	72 3	1 9	8 4	20	9 0	16 0	9 0	143	3 7
A.B	349	11 3	29 4	1 0	6 1	20	9.2	13 0	10 0	90	2.9
S F	409	8 4	8? 1	1 7	11.8	25	6 6	11 8	7 0	10?	2.1
H G	48-	12 0	110 6	2 7	23 5	60	7 8	16 0	T¶	150	3 7
S C	515	8 9	64 5	1 1	9 0	15	8 0	18 5	9 0	115	2 0
B H	655	17 3	31 8	8	8 9	24	9 6	11 4	5 4	103	2 7
W W	330	11 4	71 1	2.5	23 5	80	6 0	10 6	4 8	84	2 9
P.S	619	13 1	68 0	1 4	13 4	30	8 4	11 8	10 0	126	2.7
J K.	515	9.3	78 7	1 4	14 1	.25	8 0	14 0	9 0	128	2 3
S C.R	416	9 7	87 9	2 0	29 9	70	7 2	14 0	7 0	118	2 7
Patient mean ± SD	4?2 ± 107§	11.3 ± 2.6†	69 6 ± 24 4‖	1 7 ± 6	14 9 ± 8§	4 ± 2	8 0 ± 1 1	13 7 ± 2 5	7 9 ± 1 9	116 ± 21‡	2 8 ± 6‡
Control mean ± SD	634 ± 115	9 9 ± 2 2	110 5 ± 22.3	1 7 ± 7	32 7 ± 9 7	50 ± 10	7 6 ± 1.5	12 9 ± 1 7	8 0 ± 2 3	149 ± 52	2.3 ± .5
Control range	435-?91	8 1 1? 2	75 4 159 4	1.3 2	19 3-41.2	.30- 17	5 6-10	10 2 16	6.2 12 3	90-247	1 7 3 1

Control values represent mean ± SD and range for height and sex matched normal control subjects † = P < 0 1 ‡ = P < 0 05 § = P < 0 01 ‖ = P < 0.001 for comparison with controls.
Value below or above the control range All abbreviations are defined under Methods section.
¶ T = technically inadequate observation.

day period Urine stools and diet were analyzed for N P Na K Cl and Ca [11] Daily elemental balances (N and P in grams Na K Cl and Ca in mEq) during each period were calculated as daily intake minus daily output (urine content plus average fecal content)

Results

Phase A The several different causes of the severe malnutrition that had been present for 6 to 9 years in our patients are shown in Table I Anthropometric indices and 24 hr cr /ht ratio revealed a marked reduction in lean body mass (LBM) in all 10 patients Further indications of substandard nutrition included hypoalbuminemia (in eight of 10 patients) anemia (eight out of 10) and subnormal serum levels of carotene (three out of nine) red blood cell folate (three out of eight) magnesium (two of nine) and zinc (two of four) Serum calcium was frequently subnor

Nutritional data base A nutrition data base was completed on each subject and consisted of anthropometric data according to the method of Butterworth and colleagues[13] (height (ht) (cm), BW (Kg), per cent of standard BW TSF MAMC, 24 hr cr /ht), serum proteins (hemoglobin hematocrit (HCT), prothrombin time, partial thromboplastin time, total iron binding capacity, serum albumin (SALB), total protein, amino acid profile, and serum lipoprotein electrophoresis), minerals (serum levels of Ca (SCa) PO_4 Mg (SMg), Cu Zn (SZn), Mn Fe and 24 hour urine Zn , Mg , and Cu), and vitamins (serum levels of carotene (SCAR), ascorbic acid thiamine, B_{1}, folate and red blood cell (RBC) folate)

Cardiovascular data base The cardiovascular evaluation comprised the following studies (1) Complete physical examination, (2) standard 12 lead electrocardiogram (ECG), (3) thyroid function testing (4) standard posterior–anterior and lateral chest x rays Total heart volume was calculated from these films using the method of Keets and Enge[14] where radiographic heart volume (RHV) in ml = (length) × (breadth) × (depth) × (0 42) and (5) echocardiography (echo)

Echocardiograms were performed in the supine position on each subject as previously described[15] In each record five different complexes were analyzed and the data averaged to calculate the following variables[16] Heart rate (beats/minute) (HR) end diastolic and end systolic left ventricular wall thickness (mm) (LVWTd and LVWTs) interventricular septal thickness (mm) (IVSd) diastolic and end systolic left ventricular internal dimensions (mm) (LVIDd and LVIDs) and volumes (c c) (EdV and EsV), left ventricular mass (Gm) (LV mass), stroke volume (c c /beat) (SV), cardiac output (liters/minute) (CO) ejection fraction (EF) mean rate of left ventricular circumferential fiber shortening (circ /sec) (Vcf) per cent systolic thickening of the posterior left ventricular wall (per cent) (PWT), and left ventricular posterior wall excursion (mm) (PWE)

A pericardial effusion (PF) was considered present if an anterior and posterior epicardial to pericardial (P) echo free space was present and pericardial pulsations were absent

The relative change in absolute cardiac dimensions of cachectic patients was established by matching each phase A patient with a 'reference man or woman of the same height (± 2 cm) but of standard weight (100 per cent ± 10) The matched control subjects were healthy, young (age range 19 to 30 years) volunteers in whom the same anthropometric and cardiovascular tests were done as in the undernourished patients The absolute values for radiographic and echo ventricular volumes, mass, and cardiac output in both cachectic patients and matched controls were also normalized for BW Student s t test was used to evaluate the statistical significance of differences between the patient and control groups

Nutritional repletion Five of the 10 patients were selected for hyperalimentation (HA) on the basis that (1) nutritional repletion was believed to offer an improved prognosis, and (2) the patient agreed to a 2 to 3 month period of hospitalization on the metabolic research ward The cardiovascular data base and selected nutritional indices were determined at weekly intervals for the duration of the patient s hospitalization

HA in the present study was defined as daily nutrition furnishing per day 3 000 to 4,000 Kcal and one to three times the recommended daily allowance (RDA) of all macro and micro nutrients required by man (Table II)

Subjects entering phase B received HA by one or a combination of three routes (Table II) which have been described in earlier reports[10, 12] Route 1 is infusion of a polymeric or monomeric liquid diet (Isocal, Vivonex, Vivonex HN) via a thin nasogastric tube (NGT) (No 16 intracath) Route 2 is infusion of a 900 mosmolar nutrient solution (P_{900})[11] or lipid emulsion (intra lipid) via peripheral vein Route 3 is infusion of the 1 800 mosmolar HA solution of *Dudrick and colleagues*[10] (C_{1800}) via central vein (subclavian catheterization) The volume of solution was gradually increased over a several day period to 3 to 4 liters and continued for 2 to 5 weeks at 3 000 to 4 000 Kcal /day The daily intake of calories and nutrients administered to each subject is *given in* Table II

Metabolic balance studies Metabolic balance studies were performed during HA as previously described[17] Urine was collected in 24 hour pools and stools in 3 day pools At the end of each period, the colon was emptied by an enema Daily fecal elemental content was considered as one third of the fecal content for the corresponding 3

Table V Nutritional and cardiac responses to hyperalimentation in five malnourished patients (Phase B)*

Variable measured	Baseline	Days of hyperalimentation			
		5 15		20-35	
BW (Kg)	43 ± 11	44 ± 10	(+1%)	49 ± 8	(+12%)
24 hr cr (mg)	5?5 ± 148	630 ± 183	(+20)	67? ± 18 §	(28%)
Blood pressure (mm /Hg)	98/68	97/60		98/63	
RHV (c c)	563 ± 1?9	668 ± 232	(+19%)	70? ± 254	(+25%)
EdV (c c)	65 ± 20	77 ± 19	(+?0%)	103 ± 21†	(+59)
LV mass (Gm)	109 ± 16	126 ± 24‡	(+15%)	143 ± 36	(+31%)
HR (beats/min.)	8? ± 15	89 ± 10	(+8%)	93 ± 5	(+13%)
SV (c.c)	47 ± 14	57 ± 12	(?1%)	80 + 18‖	(68%)
CO (L/min)	3 9 ± 1 6	5 1 ± 1 5‡	(31%)	7 4 ± 1 4‖	(+90%)
EF	74 ± 0	?5 ± 08	(+1%)	72 ± 03	(-3%)
PF	0/5	1/5		2/5	

*Values represent mean ± SD Brackets enclose per cent increase over baseline value Serial chest rays available on three out of five subjects
† = P < 1 ‡ = P < .05 § = P < 01 ‖ = P < 001 for comparison with baseline value All abbreviations are defined under Methods

corrected SV and CO were elevated 8 and 25 per cent respectively above control values Systolic ejection phase indices of left ventricular function viz EF Vcf PWE and PWT were normal or in some cases significantly elevated compared to control values No patient examined in phase A had a pericardial effusion

Phase B Selected variables that illustrate changes in the nutritional and cardiovascular status of the five patients who received HA are contained in Table V These data show progressive improvement in BW and lean body mass (24 hr cr excretion) during therapy BW increased by 0 3 ± 0 11 kilogram/day In addition strongly positive metabolic balances were noted for N (+10 3 ± 1 8 Gm /day) P (+0 27 ± 06 Gm / day) Na (+57 8 ± 15 3 mEq /day) K (+35 5 ± 10 2 mEq /day) Cl (+54 3 ± 16 3 mEq /day) Ca (+313 ± 57 8 mg /day) and Mg (+5 1 ± 52 mEq /day)

The cardiovascular status of these patients also changed during the HA phase During the first 5 to 15 days of therapy intracardiac volume expanded rapidly thus RHV and EdV both increased by 20 per cent over baseline In contrast LV mass enlarged by only 15 per cent Absolute SV and CO also increased during this period by 21 and 31 per cent respectively The cardiac index increased and exceeded the normal range in three of the five cases During the next 3 weeks ventricular volumes CO and SV continued to increase gradually In contrast LV mass increased only by about 10 per cent of the initial phase A value per week EF and Vcf remained within the normal range throughout HR remained unchanged or increased slightly during HA and the initial phase A blood pressures which averaged only 98/68 were stable throughout

Two patients (W W and B H) developed physical signs and symptoms of congestive heart failure at approximately 20 and 30 days of HA respectively Both patients were treated with diuretics HA was terminated in one and both responded with clearing of signs and symptoms In the remaining three subjects no clinical evidence of congestive heart failure was detected

A pericardial effusion developed on day 20 in two subjects (W W and P S) but in both cases partial resolution occurred by day 30

The results of phase B studies in one patient are presented here in detail to illustrate the course of HA Patient W W a 36 year old woman with psychogenic anorexia had lost 60 pounds over an 8 year period Initial evaluation showed severe PCU (60 per cent of standard BW) with anemia Absolute RHV echo EdV LV mass and CO were 50 35 34 and 48 per cent less than corresponding values of her height matched control subject When those variables were indexed for BW however the values were 3 33 34 and 11 per cent greater than the corresponding weight adjusted values from the matched control EF and Vcf were decreased by 5 per cent

Table IV Echocardiographic evaluation of left ventricular function in malnourished patients (Phase A)

Patient	HR (beats/min)	SV (c c)	SV/BW (c c /Kg)	CO (L /min)	CO/BW (L /min / Kg)	EF	Vcf (circ /sec)	PWE (mm)	PWT (%)
H C	77	63 9	1 7 *	4 9	13**	89 *	1 7*	13 0**	77 8
A B	86	23 3*	8	2 0*	07	79	1 4	9 8	5?
S F	67	70 3	1 4	4 7	10	86 *	1 6 *	16 0**	,8 8
H G	119*	74 6	1 9**	8 9**	20**	82*	1 6 *	14 2*	105*
S C	90 *	53 5*	9	4 8	08	83**	1 7**	14 5 *	131 3**
B H	83	22 9*	6	1 9*	05*	72	1 3	8 4*	18 8
W W	60	47 6*	1 6**	2 9*	10	68	1 0	9 4*	76 7
P S	78	54 6*	1 2	4 3	09	80	1 4	12 0**	40 5*
J K	60	64 6	1 2	3 9	07	82**	1 7*	13 0	75
S C R	100*	58 0	1 3	5 8	13**	66	1 2	10 5	97
Patient mean ± SD	82 ± 18 3†	53 3 ± 17§	1 3 ± 4	4 4 ± 2	10 ± 03	80 ± 08‡	1 5 ± 2‡	12 1 ± 2 5†	75 3 ± 32
Control mean ± SD	68 3 ± 11	77 9 ± 5	1 2 ± 4	5 3 ± 1 2	08 ± 02	72 ± 04	1 2 ± 2	10 5 ± 6	70 8 ± 18.9
Control range	54 86	56 1 112	0 9 1 5	3 6-7 1	06 1	63 80	0 9 1 4	9 6-11 2	51 103

Control values represent mean ± SD and range for height and sex matched normal control subjects.
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mal (five of 10), but was proportional to the reduction in serum albumin *None of the five or* six patients evaluated for deficiency of thiamine, B_{12} or essential fatty acids had abnormal serum levels of these factors

The cardiovascular examination demonstrated sinus tachycardia in two subjects and pedal edema in three other individuals These physical findings were thought to be the result of anemia, hypoalbuminemia and the underlying disease processes rather than manifestations of cardiac dysfunction There were no other signs of cardiac failure in the phase A patients The ECG's did not contain significant abnormalities

RHV data *and echo variables describing* cardiac dimensions in phase A patients are presented in *Table III Chest x ray examinations* revealed a small cardiac silhouette and the calculated RHV in the cachectic group was 37 per cent smaller than in the control group (P < 01) However, when RHV was expressed per kilogram of BW, the heart in cachectic subjects was 14 per cent larger (P < 1) than in control subjects RHV is a combination of two compartments muscle and fluid (the latter comprising intracardiac chamber volume and the pericardial-epicardial sac) The echocardiogram can determine *representative indices of these subcompartments* and thereby define their contribution to a small *RHV LVWTd and IVSd measurements did not* differ significantly from undernourished and control subjects When compared to control subjects, echo LV mass in absolute terms was decreased by 22 per cent (P < 05), but when expressed per kilogram of BW LV mass was actually increased by 22 per cent (P < 05) Total left ventricular chamber volumes were also decreased, e g , EdV by 37 per cent (P < 001) and EsV by 54 per cent (P < 01) When corrected for BW, EdV was unchanged from control and EsV *was decreased by only 26 per cent (N S)*

Echo variables describing left ventricular func*tion for patients in phase A are presented in* Table IV HR was 20 per cent faster in malnourished patients (P < 0 1) The *absolute* SV was decreased by 32 per cent (P < 01) and thus absolute *CO was depressed by 17 per cent* compared to height matched controls The output values *showed considerable variability* (e g one patient had an elevated output) and the mean CO of the malnourished *group did not differ* significantly from the control mean The BW

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Variable measured	Baseline	*Days of hyperalimentation*			
		5 15		*20-35*	
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S C	90 *	53 5*	9	4 8	08	83**	1 7**	14 5	131.3 *
B H	83	22 9*	6*	1 9	05*	72	1 3	8 4*	18.8*
W W	60	47 6*	1 6**	2 9*	10	68	1 0	9 4*	76 7
P S	78	54 6*	1 2	4 3	09	80	1 4	12 0 *	40 5*
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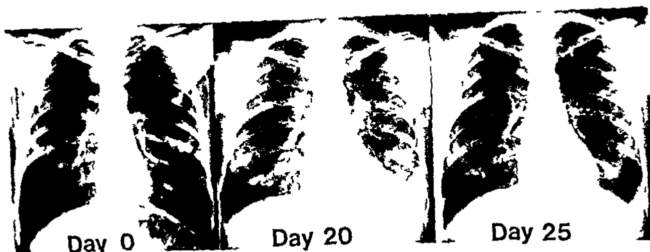


Fig 2 Radiographic changes in patient W W during HA Note small cardiac silhouette on day 0 pleural effusion and interstitial edema on day 20 the latter abnormalities resolving by day 25 See *Fig 1* and text for discussion

affect the cardiovascular system and this factor should be considered in the interpretation of our results Secondly echo has not previously been used to evaluate the hearts of cachectic subjects The third new aspect was the use of recently developed HA techniques which led to a more rapid reversal of the cachectic state than was previously possible

Phase A data from our malnourished patients showed that the reduction in heart volume measured both by radiography and echo was proportional to the loss in BW The echo data indicate that about 60 per cent of this loss in volume represents a reduction in internal chamber volume of the heart and about 40 per cent reduction in cardiac muscle mass The cardiac mass although sharply reduced had decreased to a lesser degree than the remaining lean body mass i e the heart had been partially spared For example although the absolute LV mass was approximately 22 per cent smaller than in matched normal subjects the total BW was diminished by 40 to 45 per cent and consequently the LV mass index was 124 per cent of normal The reduction in absolute cardiac mass during malnutrition might represent either (1) pathological wasting of myocardium due to impaired protein synthesis or (2) an adaptive response to the reduced blood volume and the reduced CO requirements of the wasted patient If the loss of cardiac mass is a pathological wasting process the partial sparing could be related to two interesting features of heart muscle Cannels and colleagues[8] showed that rat hearts can maintain protein synthesis by utilizing oxidizable non carbohydrate substances such as fatty acids ketone bodies acetate lactate and pyruvate This phenomenon is not observed in skeletal muscle Secondly Goldberg and co workers[9] have shown an increase in amino acid uptake and a decrease in protein catabolism in proportion to contractile frequency (and work) in the diaphragm and soleus muscle of rats If the latter muscle is subjected to an increased workload an absolute increase in mass will develop even during starvation and negative N balance The degree of cardiac atrophy in starvation might therefore be the net result of factors diminishing or augmenting cardiac work (i.e reduced blood pressure smaller blood volume and hypometabolism versus anemia and hypermetabolism)

Absolute EdV was reduced in our cachectic subjects but was proprotional to BW e g EdV/BW was 1 7 in the patients and was also 1 7 in the matched controls Three conditions present in our patients favored a smaller EdV

1 EdV is a subcompartment of the plasma volume and might therefore be expected to change in proportion to alterations in the latter Measurements of plasma volume relative to BW in starving subjects have shown this ratio to increase remain normal or decrease depending on the severity of disease[5] Dehydration diarrhea and vomiting present in some of our subjects would all tend to cause contraction of plasma volume and therefore of EdV

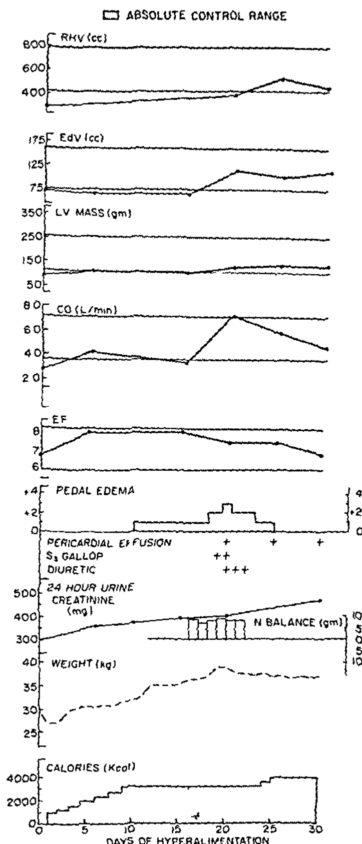


Fig 1 Nutritional and cardiovascular changes during HA in patient W W Repletion of lean body mass was demonstrated by positive increments *in weight N Balance and 24 hr cr* excretion Course was uneventful until week 3 when edema elevated CO and S gallop required treatment with diuretics CHF resolved and HA was continued through fourth week See text for further discussion All abbreviations are defined under Methods section

compared to the control subject Her oxygen consumption was 150 c c /minute A nasogastric tube (No 16 intracath) was inserted, and she was given increasing volumes of an Isocal drip (18 hours/day) over a one week interval until the maintenance dose of 3,200 calories/day was reached (Fig 1) Her nutritional course was characterized by steady gain in BW and in lean body mass (reflected in 24 hr cr shown in Fig 1) and by strongly positive balances for N, P, K, Na, and Cl The first 18 days of repletion were uneventful except for the appearance of 1+ pedal edema on day 10 On days 19 and 20, dyspnea, tachycardia a ventricular diastolic gallop left pleural effusion, radiographic interstitial pulmonary edema (Fig 2) and pedal edema all appeared The increase in RHV compared to phase A was shown by echo to be due to three components LV mass and EdV had both increased 50 to 60 per cent over the pre HA value and a pericardial effusion had developed The CO and cardiac index compared to the pre HA state had increased by 155 per cent and 90 per cent, respectively Oxygen consumption had increased by about 30 per cent over the initial value Ejection phase indices of left ventricular performance remained normal She was treated with a diuretic (chlorthalidone 50 mg) for 3 consecutive days resulting in weight loss (1 5 kilograms) and disappearance of dyspnea, tachycardia edema and the gallop rhythm Absolute CO returned to the normal range but cardiac index remained elevated HA was continued for an additional 10 days and the remainder of her hospitalization was uneventful When the echo obtained after 25 days of HA was compared to the baseline study (Fig 3), a large increase in left ventricular chamber volume and a small pericardial effusion was evident The pericardial effusion persisted until discharge LV mass continued to increase and at 4 weeks was only 3 per cent less than that of her height matched control subject

Discussion

The present investigation differs in three respects from previous studies of malnutrition and the heart First the patients in this study represent malnutrition secondary to a serious underlying primary disease process In this group the primary disease process (e g cirrhosis metastatic cancer and associated severe anemia) may

Consequently cardiac index became further elevated during the first 10 days of HA and remained above normal during the entire course of observation increasing to as much as 250 per cent of baseline in some subjects at 3 to 4 weeks LV mass index on the other hand remained relatively unchanged throughout the course of HA this means that repletion of LV mass was proceeding at the same rate as repletion of lean body mass

The rapid rise of CO and cardiac index could have resulted from two mechanisms that would increase venous return (1) over expansion of the extracellular fluid compartment and (2) hyper metabolism

1 Hyperexpansion of the extracellular fluid during HA may arise from either excessive sodium infusion or reduced excretion by the kidney in cachexia Edozien and Rahim Khan[9] found that milk protein administered to children with PCU in a 5 Gm /Kg dose caused expansion of the plasma volume and was associated with con gestive heart failure in 20 per cent of these children When salt and protein were restricted or when diuretics were added to the high protein regimen heart failure became rare The sodium intake (2 to 4 Gm /day) in our subjects did not appear excessive Balance ratios (e g $\Delta Na/\Delta N = 5.6$ $\Delta Na/\Delta BW = 16.7$) suggest however that extracellular fluid may have expanded out of proportion to muscle protoplasm as the theoretical values based on repletion of lean body mass with normal composition are 0 77 and 2 6 respectively[31] Excessive expansion of extracellular fluid during HA could have resulted from subnormal renal excretion of NaCl as described by Alleyne[2] in children with PCU

2 There is also evidence that a large CO during repletion can result from increased metabolic demands In both adults and children with malnutrition basal metabolic rate increases rapidly during repletion and sometimes exceeds the normal expected value[3] In two of our patients in whom basal metabolic rate was measured during HA increases in CO closely paralleled those in metabolic rate

Two of our five patients developed congestive heart failure during the period of high CO associated with HA while the others remained compensated Cardiac decompensation under these conditions presumably resulted from a rapidly expanded plasma volume and augmented metabolic rate which overloaded the small left ventricle It remains possible that the contractile reserve was also depressed in these hearts It is unfortunate in this regard that little is known regarding the intrinsic biochemical and ultra structural disturbances of the myocardium in malnutrition and how these factors may be altered by HA

Summary

The effect of PCU and HA on heart dimensions and function was examined with non invasive methods in 10 patients with severe undernutrition of diverse etiology Control subjects were 10 normal men and women matched to their cachectic counterparts by height and sex

The study was conducted in two phases In phase A baseline studies of heart dimensions and function were completed Phase B consisted of cardiovascular and metabolic monitoring during 4 to 6 weeks of enteral or parenteral HA

Phase A was characterized by a reduced radio graphic total heart volume echo EdV, LV mass and CO These reductions however were only one half to one eighth as great as the losses in BW The patients therefore entered HA with an elevated LV mass index and cardiac index Ejection phase indices of LV function (EF and Vcf) were normal or enhanced

Phase B studies in five subjects showed that decreased cardiac size and output were correctible by HA but at differing rates Ventricular volume and CO corrected more rapidly than LV mass under the conditions of rapid repletion where the daily sodium intake was 2 to 4 grams and values for cardiac index reached 250 per cent of normal Resting metabolic rate also increased during phase B The combination of an elevated output excessive sodium retention and increased metabolic rate while LV mass was still reduced appeared to be responsible for cardiac decompensation in two of five repleted patients

To prevent cardiac decompensation during the HA of undernourished subjects we propose the use of low salt regimens a slower rate of HA and serial monitoring of cardiac dimensions and function by clinical examination and echo

We wish to thank Mr John Perkins for his assistance with the echocardiograms and Dr Daniel Rudman for his valuable criticism in preparing this manuscript

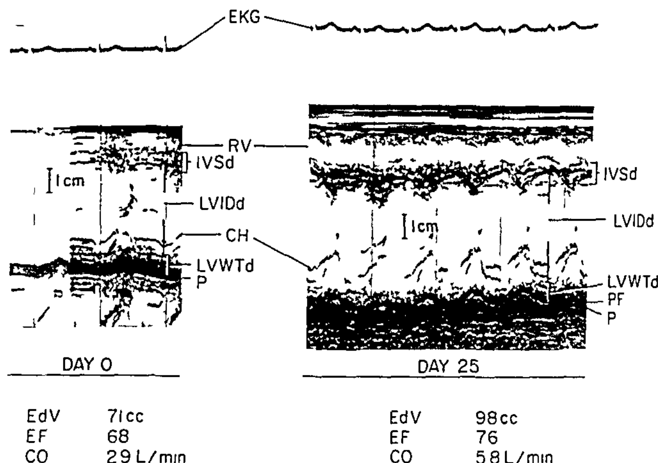


Fig 3 Echo changes in patient W W during HA Note marked increase in chamber dimensions and calculated CO on day 25 compared to day 0 See *Fig 2* for corresponding chest x rays and *Fig 1* and text for clinical course All abbreviations are defined under Methods section

2 A decreased absolute CO would tend under most conditions to reduce venous return regard less of blood volume size

3 Also tending to reduce EdV was a 20 per cent faster HR in the cachectic than in the control subjects

We have also demonstrated that absolute CO was reduced in the malnourished patients This reduction was less than the reduction in lean body mass and therefore resulted in an elevated cardiac index Furthermore indices of ventricular function were normal or enhanced, suggesting that a relative hyperdynamic circulatory state was present This is in contrast to uncomplicated starvation, where CO and EF have been reported to be depressed [5, 7] Several conditions would tend to promote an increased cardiac index and cardiac work in our patients with nosocomial protein–cal orie starvation, e g anemia in eight liver disease in one and the possibility of cancer hypermeta bolism in three [20] An alternative explanation for the enhanced ventricular function indices is based on the requirement for ventricular shortening to be maintained or increased in order to maintain SV as ventricular EdV is decreased EdV fell by 37 per cent whereas SV fell by 32 per cent in our patients This suggests that EF and shortening indices would have to be preserved or actually increase to produce the observed SV *Myocardial contractile state could not be directly assessed* in the present study of intact patients, but the normal or augmented values for Vcf in the presence of normal systemic arterial blood pres sure suggests that contractility was not de pressed

During HA the reductions in LV mass EdV, and CO were all repaired but at different rates Intracardiac volume and CO increased promptly and were largely corrected within 2 weeks On the other hand, LV mass increased relatively slowly The absolute level of EdV and CO had returned to the control range by 1 to 2 weeks whereas LV mass showed only a small change over this period and after 5 to 6 weeks was still below the normal range BW was also repaired slowly, at a rate of about +5 per cent of initial BW per week

Consequently cardiac index became further elevated during the first 10 days of HA and remained above normal during the entire course of observation increasing to as much as 250 per cent of baseline in some subjects at 3 to 4 weeks LV mass index on the other hand remained relatively unchanged throughout the course of HA this means that repletion of LV mass was proceeding at the same rate as repletion of lean body mass

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Hemodynamic evaluation of the Ionescu-Shiley pericardial xenograft in the mitral position

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Glutaraldehyde treated pericardial xenografts have been used for heart valve replacement during the past 6 years Clinical results have been extremely gratifying Very low thrombogenicity without anticoagulant therapy is one of the important benefits of this type of valve replacement This report presents the results of a late hemodynamic evaluation of 27 patients and of sequential studies of six patients who had mitral valve replacement with the Ionescu Shiley pericardial xenograft *

Patients and methods

Since March 1971 106 patients had mitral valve replacement with pericardial xenografts Actuarial survival and event free curves are shown in Fig 1 Four embolic episodes were noted in the entire series All were mild or trivial occurred within the first 6 weeks following valve replacement and left no sequelae Clinically 94 per cent of patients were in Grade I (NYHA) at the latest assessment

Twenty seven patients underwent hemodynamic evaluation at a mean duration of 40 3 ± 2 8 (range 24 to 59) months following valve insertion The criteria for selection were an interval of at least two years from valve replacement and the informed consent of the patient

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*Shiley Laboratories, Irvine California

The annulus diameter of the grafts used was 25 mm in two patients 27 mm in 15 patients and 29 mm in 10 patients The clinical details of these patients are shown in Table I Six patients had in addition to the preoperative investigation two separate hemodynamic studies performed at mean intervals of 11 2 (± 1 6) and 42 8 (± 3 3) months following pericardial xenograft implantation Of the 20 patients who had preoperative cardiac catheterization 10 had resting pulmonary artery systolic pressure greater than 60 mm Hg

All patients were hospitalized 24 hours prior to hemodynamic study On admission a detailed clinical history estimation of functional capability physical examination hematological assessment a chest radiograph a 12 lead electrocardiogram and a phonocardiogram were obtained in all patients Electrocardiograms and chest radiographs were analyzed for rhythm left ventricular voltage (using the sum of SV and RV_5) and cardiothoracic ratio Right and left heart catheterization was performed in the postabsorptive state without any prior sedation Pulmonary and systemic pressures were transduced by strain gauge manometers (SEM 486) with the zero level set 5 cm below the sternal angle integrated electronically and recorded on a multi channel ultraviolet light recorder (SEM* 3012) Cardiac output was measured by the direct Fick method using 2 minutes of gas collection Hemodynamic data were obtained during a 4 minute period of rest and between the fourth and sixth minute of a 6-minute period of supine leg exercise on a bicycle

*She lds a d Fpstein Mon toring Middlese U K

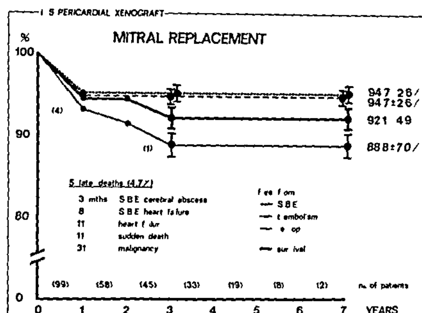


Fig 1 Actuarial analysis of results following mitral pericardial xenograft valve replacement The data are expressed as per cent expected survival rate and individual event free curves for complications

Table I Preoperative clinical details

	Number of patients
Male	8
Female	19
Age	
Mean	43 6 yrs (±1 8)
Range	19 62 yrs
Clinical lesion	
Stenosis	9
Incompetence	6
Mixed	12
Rhythm	
Atrial fibrillation	19
Sinus rhythm	8
Functional status (NYHA)	
II	6
III	19
IV	2
Previous closed mitral valvotomy	12

ergometer Left ventricular angiograms were performed in all patients at the end of the study

Pulmonary vascular resistance was calculated using the standard formula The mean diastolic gradient across the pericardial xenograft was measured by planimetric integration of at least five simultaneously recorded phasic left ventricular and pulmonary wedge tracings The xenograft surface area was calculated according to the hydraulic formula of Gorlin and Gorlin

Results

Electrocardiographic and radiological changes The mean cardiothoracic ratio showed a significant decrease from a preoperative level of 0 59 to 0 54 at the postoperative study ($p < 0\,001$) The mean left ventricular voltage was 34 8 mm preoperatively and 33 8 mm at the postoperative study This difference was not statistically significant

Hemodynamic findings at rest The results are given in Tables II and III

The mean cardiac index showed a significant increase from a preoperative level of 1 9 L/min/M^2 to 2 6 L/min/M^2 at the postoperative study ($p < 0\,001$) The oxygen uptake also showed a smaller but still significant rise ($p < 0\,05$) The mean pulmonary artery and wedge pressures were significantly reduced at the postoperative study ($p < 0\,001$) with a corresponding reduction in mean pulmonary vascular resistance ($p < 0\,01$) Postoperatively, the mean diastolic gradient across the xenograft was 6 4 (± 0 5) mm Hg and the calculated xenograft surface area was 2 0 (± 0 1) cm^2 The results obtained in 10 patients with severe preoperative pulmonary hypertension are presented in Table III This group of patients showed reductions in mean pulmonary artery and wedge pressures and in pulmonary

Table II Pre and postoperative hemodynamic data (Mean values ± SEM) of 27 patients with pericardial xenografts in the mitral position

	O uptake (ml /min /M)		*Cardiac index (L /min /M)*		*PW̄P (mm Hg)*		*PĀP (mm Hg)*		*PVR (dynes sec cm M)*		*Mean diastolic gradient (mm Hg)*		*Calculated xenograft surface area (cm)*	
	R	*E*	*R*	*E*	*R*	*F*	*R*	*E*	*R*	*E*	*R*	*E*	*R*	*E*
Preop	123 7	314 6	1 9	3 0	23 3	40 4	38 7	57 1	535 6	656 8	–	–	–	–
	±6 0	±40 4	±0 1	±0 3	±1 9	±2 7	±4 1	±4.9	±113 3	±241 1	–	–	–	–
Postop	136 3	406 5	2 6	4 1	13 8	29 4	22 8	4?0	285 0	?60 3	6 4	15 3	2 0	2.3
	–4 0	±14 4	±0 1	±0 2	±0 8	±1 5	±1 0	±1 9	±20 7	±26.3	±0 5	±0 9	+0 1	±0 1
p value	<0 05	<0 05	<0 001	<0 01	<0 001	<0 01	<0 001	<0 01	<0 01	<0 05				

Abbreviations SEM = standard e r of the mean PWP = mean pulmonary wedge pressure PĀP = mean pulmonary artery pressure PVR = pulm nary vasc lar resistan R = rest E = exer ise

Table III Hemodynamic data in 10 patients with preoperative resting pulmonary systolic pressure > 60 mm Hg (Mean values ± SEM)

	O uptake (ml /min /M)		*Cardiac index (L /min /M)*		*PW̄P (mm Hg)*		*PĀP (mm Hg)*		*PVR (dynes sec cm M)*	
	R	*E*	*R*	*E*	*R*	*E*	*R*	*E*	*R*	*E*
Preop	112 6	308 5	1.9	2 8	27 7	44 5	50 4	66 3	599 8	834
	+5 9	±50 1	±0 ?	±0 5	±2 9	±2 2	±6 2	±5 9	±163 7	±239 8
Postop	13/ 7	39 6	2 7	4 3	15 6	29 8	25 2	44	294 5	?88 9
	±7 7	±19 3	±0 2	±0 3	±1 2	±2 7	±1 8	±3 9	±30 7	+55 2
p value	<0 05	<0 05	<0 01	<0 01	<0 001	<0 01	<0 001	<0 01	<0 01	<0 01

Preoperat exe cise t dies l ble in ix pati nts nly
Abbreviati ns SEM = st nd rd rro of the me PWP = m n p lmo ry wedg pressure PAP = mean pulmo ary artery pressure PVR = pulm n ry ascula resistan R = est E = ercise

vascular resistance comparable to those found in patients with a lesser degree of pulmonary hypertension Thus in this series the severity of pre existing pulmonary hypertension did not seem to influence the postoperative hemodynamic im provement

Hemodynamic findings on exercise The cardiac index increased significantly from a preoperative level of 3 0 L /min /M² to 4 1 L./min /M postoperatively ($p < 0\ 01$) For each milliliter increase in oxygen uptake the cardiac index rose 5 6 ml The mean pulmonary artery and wedge pressures showed significant reduction ($p < 0\ 01$) from the preoperative values but were still abnormally elevated The pulmonary vascu lar resistance also showed significant reduction from the preoperative level ($p < 0\ 05$) Those patients with severe pulmonary hypertension preoperatively showed a similar improvement in cardiac output pulmonary pressures and vascu lar resistance Mean diastolic gradient increased from a resting value of 6 4 mm Hg to 15 3 mm Hg on exercise The calculated surface area showed an increase with exercise to 2 3 cm

Sequential studies One preoperative and two separate postoperative studies were performed in six patients These hemodynamic investigations were carried out under identical physiological conditions and the results are presented graph ically in Figs 2 and 3 At the first postoperative study the cardiac index mean pulmonary artery and wedge pressures and pulmonary vascular resistance showed a significant improvement both at rest and on exercise when compared with the preoperative data The improvement was similar to that obtained in the entire group of patients as described in the previous para graphs

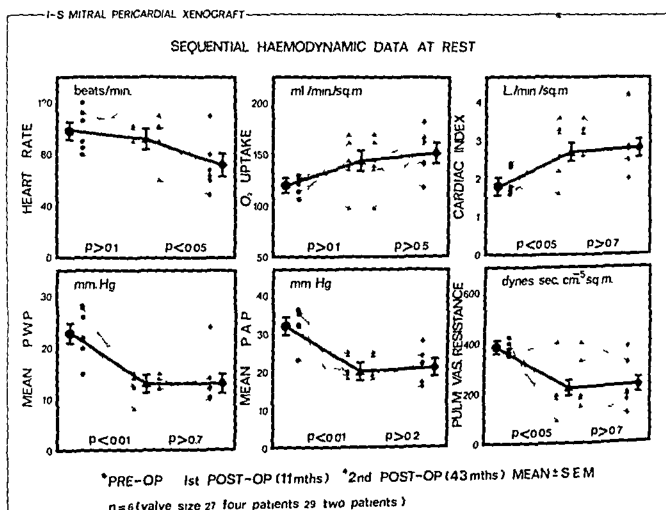


Fig 2 Sequential hemodynamic data at rest from six patients with mitral pericardial xenograft *Mean PWP* = mean pulmonary wedge pressure *O Uptake* = oxygen uptake *Mean PAP* = mean pulmonary artery pressure *Pulm Vasc Resistance* = pulmonary vascular resistance *SEM* = standard error of the mean

There were no significant changes in cardiac index pulmonary artery and wedge pressures and pulmonary vascular resistance between the first and the second postoperative study

The mean diastolic gradient across the xenografts were 7 1 mm Hg at rest and 20 1 mm Hg on exercise at the first and 6 6 mm Hg and 19 1 mm Hg at the second postoperative study This difference was not significant The calculated xenograft areas were 2 2 cm ^{2} at rest and 2 6 cm ^{2} on exercise at the first postoperative study A marginal increase to 2 3 and 2 7 cm ^{2}, respectively was noted at the second postoperative study, but again the difference was not significant

Left ventricular angiography Left ventricular angiograms demonstrated competent pericardial xenografts in all patients

Discussion

The pericardial xenograft was primarily created to minimize the rate of thromboembolism traditionally associated with prosthetic replacement of the mitral valve The experience during the past 6 years has demonstrated that, even without the use of anticoagulants this aim has been attained[1] The structural integrity of the xenograft has been maintained as shown by six years of clinical follow up and by over seven years of fatigue testing in vitro

The results of this study demonstrated that mitral valve replacement with pericardial xenografts produced significant hemodynamic improvement and that this improvement was maintained for periods of up to 59 months following valve insertion The study also confirmed the previously reported reversibility of pulmonary hypertension following mitral valve replacement[5 6]

The results showed that although a postoperative increase in cardiac output and in oxygen uptake was demonstrated both at rest and during exercise the hemodynamic response to exercise

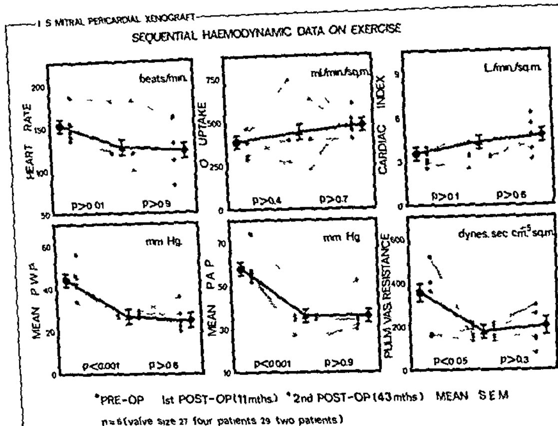


Fig 3 Sequential hemodynamic data on exercise from six patients with mitral pericardial xenograft Abbreviations as in Fig 2

was still impaired Postoperatively the mean pulmonary artery and wedge pressures approached normal figures at rest but rose to abnormal levels with exercise This seems to be a universal finding with all types of mitral valve replacement[3] and it may be related to the fact that all valve substitutes inserted in the mitral position produce some degree of obstruction to forward flow especially during exercise The mean diastolic gradient across the mitral pericardial xenograft of 6 4 mm Hg compares favorably with gradients obtained with other mitral valve substitutes

Published results of postoperative hemodynamic evaluations of other currently used mitral valve replacements are given in Table IV These data provide only a perspective against which the results of the present study can be considered Direct comparison between results obtained with various valve substitutes is difficult due to the differences in the methods of study and the diversity of patient population Furthermore only scanty reports of late hemodynamic evaluations are available the majority of these having been performed at less than 18 months postoperatively as compared with 40 months in the present study Nevertheless the data presented in Table IV show that hemodynamically the pericardial xenograft compares favorably with other types of valve substitute used in the mitral position

Although the number of patients with sequential hemodynamic investigations was small the results are of considerable importance They established that maximum circulatory improvement was obtained by the end of the first year following valve insertion and that the functional integrity of the xenograft was maintained intact with the passage of time Similar results were obtained from investigations performed on patients with pericardial xenografts in the aortic position[7]

In conclusion this study has demonstrated significant hemodynamic improvement following mitral valve replacement with the Ionescu Shiley pericardial xenograft and maintenance of valve

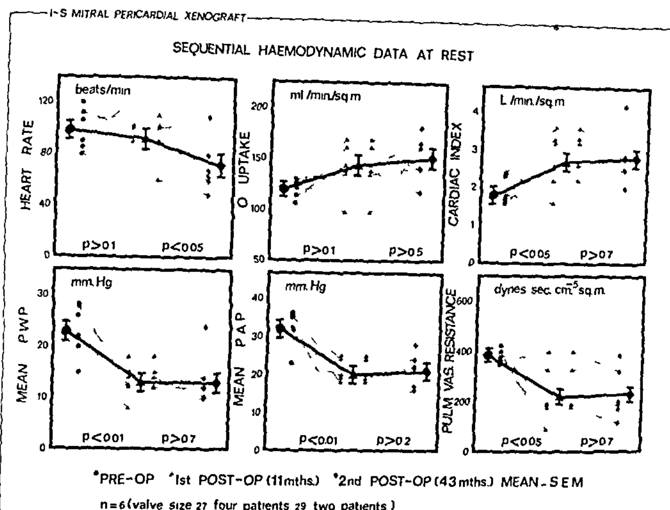


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Table IV Hemodynamic results following mitral valve replacement with different types of valve substitutes

Authors	Mitral valve substitute	Time of study (months postop)	Cardiac index (L /min /M ²)		Mean PWP (mm Hg)		Mean diastolic gradient (mm. Hg)	
			R	E	R	E	R	E
Pietras et al[3] (1974)	Starr Edwards valve Model 6300	16 3	3 2	4 8	13.2	30	11 6	24 5
Haerten et al (1976)	Starr Edwards valve Model 6300	12	2 0	3 4	14	26	7 2	
Bjork et al (1974)	Bjork Shiley valve-							
	50 angle	5 13*	4 6†	7 4†	16 7	30 4	4 3	11 7
	60° angle	5 13	4 4†	7 9†	16 9	25 8	4 7	8 4
Haerten et al (1976)	Lillehei Kaster valve		2 0	3 4	14	29	6 2	
Sigwart et al [2] (1976)	Lillehei Kaster valve	1 6*	3 0		16		9	
Johnson et al (1975)	Hancock porcine xenograft	5 5	2 6		17		6 5	
Lurie et al[1] (1976)	Hancock porcine xenograft	1 15*	2.5		15		8	
Present study	I S pericardial xenograft	40 3	2 6	4 1	13 8	29 4	6 4	15 3

Mean period not available
†Cardiac output
Abbreviations PWP = pulmonary wedge pressure R = rest E = exercise

function up to 59 months postoperatively Repeat circulatory investigations will be performed at longer intervals in order to continually appraise the function of this valve

Summary

Hemodynamic studies were performed in 27 patients at a mean interval of 40 3 (range 24 to 59) months following mitral valve replacement with pericardial xenografts Six patients had sequential studies one before operation and two separate investigations at mean intervals of 11 2 and 42 8 months following valve replacement

The results showed significant increase in cardiac index reduction in mean pulmonary artery and wedge pressures and decrease in pulmonary vascular resistance both at rest and during exercise when compared with the preoperative values The mean diastolic gradient across the pericardial xenografts was 6 4 mm Hg at rest and 15 3 mm Hg during exercise The calculated xenograft surface area was 2 0 and 2 3 cm ², respectively

The sequential studies established that the maximum hemodynamic improvement was achieved within the first year following valve replacement and that the functional performance of the xenografts was maintained unaltered with the passage of time

We wish to thank Miss Anne E Tunnicliffe for help in the preparation of this manuscript

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associates[26] After taking the preparations the subjects were given a light standardized breakfast The same parameters were then registered again 30 minutes later and thereafter at hourly intervals throughout an observation period of five hours In addition after 1 2 and 5 hours exertion tests of five minutes duration were performed on the bicycle ergometer at the previously determined individual workloads During exercise and during the recovery phase the E C G was monitored continuously on a direct writer

Starting 30 minutes before the administration of the preparations continuous E C G recordings were made over an average period of 5¾ hours on a single channel battery powered portable tape recorder (Holter Avionics Model 400 Electrocardiocorder)[1] The self adhesive electrodes were fixed on the midclavicular line at the fifth right intercostal space on the manubrium sterni and in the V (exploratory electrode) position The running speed of the recorder was checked to make sure that there were no fluctuations The E C G tapes were scanned on an Avionics Model 650 Electrocardioscanner at 60 times the recording speed Any significant morphological alterations appearing on the oscilloscope and any abrupt changes in heart rate were examined at normal speed and simultaneously traced out for detailed analysis at a paper speed of 25 mm/sec

In a second series of tests C 50 005/A Ba was given in a dose of 15 mg thrice daily on two consecutive days to four young volunteers aged 23 to 27 years (average 25 years) and the effects were compared with those observed after the administration of placebo on a previous occasion E C G tracings were recorded continuously for nine hours daily The subjects were instructed to pursue their normal everyday activities throughout the study

The statistical significance of the differences between any changes observed after placebo and those produced by the test substance was determined by the t test and is indicated in the figures by = $p < 0.05$ = $p < 0.01$ and • = $p < 0.001$ All the values quoted are means with the corresponding standard errors ($\bar{x} \pm s_{\bar{x}}$)

Results

Effects of single oral doses

Heart rate (Fig 1) Thirty and 60 minutes after the administration of C 50 005/A Ba there was a dose related increase in heart rate of 8 to 20

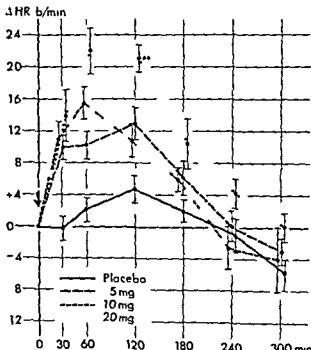


Fig 1 Changes in heart rate after single oral doses of C 50 005/A Ba (n = 8)

beats/minute above the placebo value The differences were statistically significant at all dose levels up to 120 minutes after administration The effects of doses of 5 and 10 mg C 50 005/A Ba remained demonstrable for three hours and that of 20 mg for four hours There was no statistically significant difference between the results observed in the two age groups

Arterial blood pressure (Fig 2) The effect of C 50 005 A Ba on *systolic pressure* differed in the two age groups A dose related increase occurred in both but the values 30 and 60 minutes after administration at all dose levels were distinctly higher in the younger than in the older subjects (18 to 31 as against 4 to 21 mm Hg) The increases in systolic pressure 30 minutes after the administration of the drug were all statistically significant except at the 5 mg dose level in the older group

The effect of C 50 005/A Ba on *diastolic pressure* also differed in the two age groups At all dose levels there was a more marked decrease in the younger group

The maximum effect on systolic pressure was observed after 30 minutes except at doses of 5 mg in the elder and 20 mg in the younger group The duration of effect was two hours after a dose of 5 mg and in the younger subjects up to four hours

Human pharmacology studies with a new, orally active stimulant of cardiac adrenergic beta-receptors

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In the management of heart failure substances that stimulate predominantly the adrenergic β_1 receptors could be of value as an alternative to, or in combination with, cardiac glycosides and could open up a new therapeutic approach Such drugs should have a positively inotropic effect without causing any significant acceleration of heart rate They should not induce arrhythmias, and to be widely applicable they would have to be available in both oral and parenteral dosage forms The relatively cardioselective β_1 receptor stimulant dobutamine,* though only administrable by intravenous infusion, is the first compound of this type that appears to produce beneficial effects under clinical conditions[2, 11, 16]

In investigations in animals a new experimental compound code numbered C 50 005/A Ba or H 80/62† proved to be a cardioselective β receptor stimulant satisfying the above conditions[5, 6] In man also it seems to be a selective beta 1 adrenoceptor agonist, which is in addition active by the oral route[19] The results of human pharmacology studies conducted with this preparation including information on the incidence and dependence on dosage of disturbances of cardiac rhythm, are described in the present paper

Methods

Eight male volunteers free of cardiovascular disorders who had given their informed consent to the study in writing, each received C 50,005/A Ba in 5 mg tablets in doses of 5 10 and 20 mg and a placebo, single blind and in random sequence at intervals of one week

To make allowance for the known difference in the incidence of effort induced arrhythmias due to age[21] the subjects were divided into two groups, one consisting of the four younger subjects aged between 23 and 26 years (average 24 ± 0 6 years) and the other of the elder subjects, whose ages ranged from 49 to 55 years (average 52 ± 1 5 years)

In preliminary tests on a bicycle ergometer (Elema Schonander EM 369) the individual workloads producing an increase in heart rate of 160 beats/minute in the younger group and 140 beats/minute in the elder group were determined These figures correspond to about 80 per cent of the maximum attainable heart rates in the respective age groups[17] In the morning before the preparations were taken, recordings were made of heart rate and the E C G and blood pressure was measured by the cuff method after the subjects had lain quietly for 15 minutes The E C G tracing carotid pulse wave and phonocardiogram were recorded simultaneously on a three channel writer (Cardiopan 3 T Type 703 Philips Zurich) for subsequent evaluation of the systolic time intervals according to the method of Weissler and

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*E Lilly Research Laboratories Indianapolis Ind DL-3 4-dihydroxy N [3 (4 hydroxyphenyl) 1 methyl n propyl] phenethylamine hydrochloride

†CIBA GEIGY Ltd Basel Switzerland C 50 005/A Ba AB Hässle Molndal H 80/62 1 isopropylamino-3 (p hydroxy phenoxy) 2 propanol hydrochloride hereunder referred to as C 50 005/A Ba

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of 5 mg the frequency of marked SAR increased slightly during the observation period of on the average 5¾ hours after 10 mg the average for all subjects rose from 81 (placebo and 5 mg) to 102 (n.s.) and after 20 mg to 149 ($p < 0.05$) In three subjects however the occurrence of marked SAR after the various doses of C 50 005/A Ba was no more frequent than after placebo and in some instances even less so In general not only the frequency of SARs increased but also their intensity since there was a dose related acceleration of the basic heart rate and such abrupt bradycardic phases resulted in extreme fluctuations of sinus rhythm by up to almost 50 beats/minute Between the second and fourth hours after the administration of C 50 005/A Ba but also after placebo SARs tended to be slightly more frequent otherwise they were fairly regularly distributed throughout the observation period In particular their occurrence did not specifically coincide with the maximum effect of the drug

In four subjects *transient sinus arrest* lasting for 1 1 to 1 4 seconds was observed on one or two occasions with subsequent slowing of rhythm and unchanged QRS complexes In one case this phenomenon only occurred after placebo in the other three it was noted once after 5 mg C 50 005/A Ba twice after 10 mg and once after 20 mg

Changes in the ST segment were visible in the E C G of one 55 year old subject whose tracings both at rest and during effort had been normal before treatment Twenty five minutes after a dose of 20 mg C 50 005/A Ba depressions of the ST segments by more than 1 mm appeared unaccompanied by any corresponding clinical symptomatology As can be seen in Fig 5 there was a correlation between the extent of the ST depression and that of the rise in heart rate and systolic blood pressure

Effects of repeated administration

Continuous E C G recordings (Table II) The changes in cardiac rhythm observed in four healthy young volunteers after 15 mg three times a day of C 50 005/A Ba and placebo on two consecutive days are indicated in Table II The E C G tracings recorded continuously for an average of nine hours daily showed isolated SVES in all four subjects after the placebo On the first day of treatment with C 50 005/A Ba SVES were only seen in two subjects but on the second day they were again present in all four No alterations due to treatment could be established VES did not occur after placebo medication and altogether only four were seen on the two consecutive days of treatment with C 50 005/A Ba

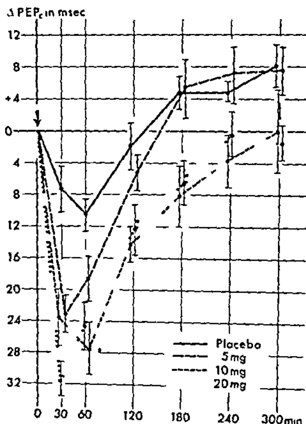


Fig 3 Changes in rate corrected pre-ejection period (PEP_c) after single oral doses of C 50 005/A Ba (n = 8)

The frequency of marked SAR increased on the first day of treatment with C 50 005/A Ba and diminished again on the second They tended to occur more often during the first hour after the first dose on the first day None of the above mentioned changes was statistically significant

Subjective tolerability Single doses of C 50 005/A Ba were subjectively well tolerated Fifteen to 20 minutes after doses of 10 mg and 20 mg six of the eight subjects experienced palpitations which usually disappeared within an hour One of the younger subjects also had a feeling of tightness in the chest and slight headaches at all dose levels

On the first day of repeated administration two of the four subjects felt slight palpitations 15 minutes after taking C 50 005/A Ba No other undesirable effects were reported

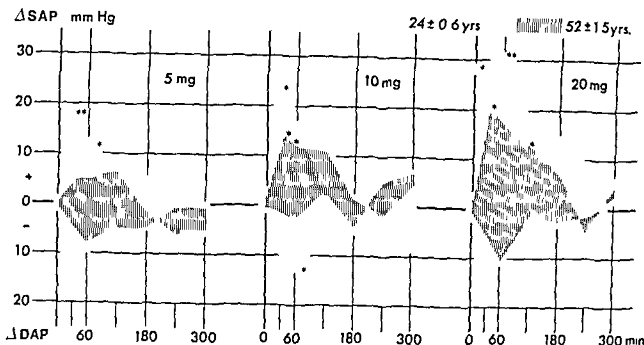


Fig 2 Changes in systolic and diastolic blood pressure in younger and elderly subjects after single oral doses of C 50 005/A Ba (n = 8)

after 20 mg The maximum effect on diastolic pressure was noted between 30 and 60 minutes after medication The decrease was slight and not dose related, and by comparison with the placebo values only significant at one determination each after 5 mg ($p < 0.05$) and 10 mg ($p < 0.01$) The duration of effect was 2 to 3 hours

Pre ejection period (PEP) (Fig 3) The changes in the rate corrected pre ejection period (PEP) which serves as an index of myocardial contractility were not significantly different in the two age groups An increase in contractility reflected in a distinct decrease of approximately 10 msec in the duration of the PEP_c and attributable to digestion was observed after placebo medication Thirty minutes after the administration of C 50,005/A Ba there was a dose related decrease in PEP In relation to the placebo values, the reductions recorded after 5, 10 and 20 mg , respectively were −16 9 msec ($p < 0.05$) −17 3 msec ($p < 0.01$), and −24 3 msec ($p < 0.001$), the corresponding 60 minute values were −8 msec (n.s) −17 msec ($p < 0.01$) and −14 msec ($p < 0.05$) Up to three hours after doses of 10 and 20 mg the reductions were significantly ($p < 0.05$) different from the placebo values The maximum increase in contractility was reached 30 minutes after 5 and 20 mg and 60 minutes after 10 mg and the duration of this effect after 10 and 20 mg was three hours

Continuous E C G recordings (Figs 4 and 5 Table I) In each of two of the eight subjects, in whom the E C G was recorded continuously over an average period of 5 3/4 hours one *ventricular extrasystole* (VES) was seen during the first exercise test after placebo medication After the administration of C 50 005/A Ba there was an on the whole slight non dose related and statistically non significant increase in the frequency of VES, *in five of the eight subjects* altogether 11 VES occurred—five in three subjects after 5 mg one in each of three subjects after 10 mg and one in each of three subjects after 20 mg Of the total of 11 VES recorded after the administration of the drug only two occurred during effort

Supraventricular extrasystoles (SVES) were *not observed after placebo* but altogether 17 appeared in five subjects after C 50 005/A Ba (seven after 5 mg , seven after 10 mg and three after 20 mg) Scrutiny of the E C G 's revealed the combined occurrence of SVES and VES in half of the tracings *Only* one of the 17 SVES arose during effort

Sinus arrhythmias (SAR) with changes in pulse rate of more than 30 beats/minute within 4 seconds were recorded in seven of the eight subjects after placebo These changes were mainly observed in the younger group and were in some cases associated with a considerable slowing of sinus rhythm, independently of respiration and without any conspicuous alteration in the P wave Prior to the change, heart rate was usually relatively fast (> 90 beats/minute) After the administration of C 50 005/A Ba except in a dose

Table I Occurrence of arrhythmias during an observation period of 5¾ hours after single oral doses of C 50 005/A Ba and placebo (n = 8)

Subj No	Activity	Placebo SVES	Placebo VES	Placebo SAR	Placebo SA	5 mg SVES	5 mg VES	5 mg SAR	5 mg SA	10 mg SVES	10 mg VES	10 mg SAR	10 mg SA	20 mg SVES	20 mg VES	20 mg SAR	20 mg SA
197	Everyday activity			3								5		2		10	
	during ergometry																
200	Everyday activity			30				16				32	1			[illegible]7	
	during ergometry							2				1					
22?	Everyday activity			18			3	20	1		1	20	1		1	25	
	during ergometry																
226	Everyday activity			14	1	2		12		1	1	8				14	
	during ergometry																
16?	Everyday activity			7		2	1	8				1		1		10	
	during ergometry																
19?	Everyday activity			2		3		9		4	1	10			1	21	
	during ergometry		1				1			1						1	
19?	Everyday activity									1		10				7	
	during ergometry		1														
224	Everyday activity			7				11				15				3[illegible]	1
	during ergometry														1		
	Total		2	81	1	7	5	78	1	7	3	102	2	3	3	147	1

$p < 0.05$
Abbreviations SVES = supraventricular extrasystoles VES = ventricular extrasystoles SAR = sinus arrhythmias SA = sinus arrest.

Discussion

Stimulation of the cardiac adrenergic β receptors leads to an increase in heart rate and myocardial contractility If the cardiostimulation is not accompanied with peripheral vasodilatation there is an increase in systolic blood pressure which through the intervention of the baroreceptors checks the acceleration of heart rate This is certainly one reason why the increase in heart rate following the administration of dobutamine[9] and also C 50 005/A Ba is generally fairly moderate A further explanation could be that there are—as various authors have postulated[2-5]—two different types of cardiac β receptor of which one predominantly mediates chronotropic and the other inotropic effects There would accordingly be β stimulants and β blockers that preferentially act on the one or the other type of receptor Evidence has in fact been adduced suggesting that this is true of certain β blockers

One as it were unexpected by product of this study was the finding that the susceptibility of the cardiac adrenergic β receptors to stimulation diminishes with age as manifested by the smaller increase in systolic blood pressure noted in the older subjects No such difference due to aging was however detectable in the increase in heart rate which in the case of preparations like C 50 005/A Ba is of course also mediated by the β receptors This can be attributed to the loss of sensitivity of the baroreceptors with advancing age[6] as a result of which the restraint on the increase in heart rate following the rise in systolic pressure was less marked in the older subjects hence no difference in the increase in heart rate in the two groups was seen for reasons not directly connected with cardiac function Whether the diminished susceptibility to β stimulation is caused by a loss of sensitivity or a decrease in the density of

Table II Occurrence of arrhythmias during an observation period of 9 hours daily on two consecutive days after 15 mg t i d C 50 005/A Ba and placebo (n = 4)

Subj No	Placebo SVES	Placebo VES	Placebo SAR	Day 1 SVES	Day 1 VES	Day 1 SAR	Day 2 SVES	Day 2 VES	Day 2 SAR
197	1		4	1		14	3		1
200	1		10			58	2		33
220	1			[illegible]	2	28	2	1	5
2?6	7		11		1	9	5		14
Total	10		25	3	3	109	12	1	53

Abbreviations SVES = supraventricular extrasystoles VES = ventricular extrasystoles SAR = sinus arrhythmias

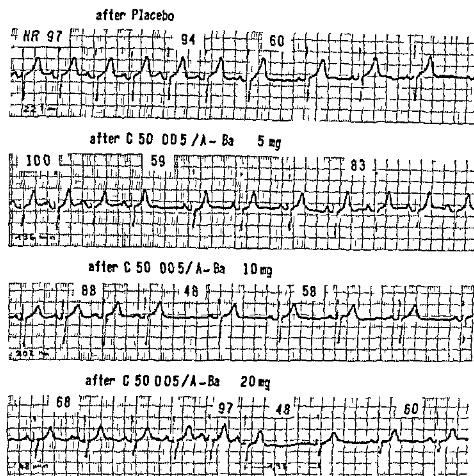


Fig 4 Accentuation of sinus arrhythmia by single oral doses of C 50 005/A Ba in one healthy volunteer

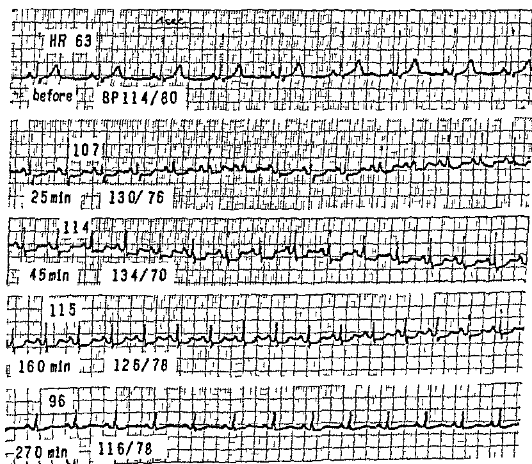


Fig 5 Depression of ST segment in a 5ὐ year old subject after a single oral dose of 20 mg C 50 005/A Ba

with diminished pumping efficiency of the heart due to reduced myocardial contractility (power failure) In patients with coronary disease however it is possible that it might increase myocardial oxygen requirement to a potentially dangerous degree The compound could presumably also afford a means of counteracting the cardiac effects of β receptor blockade in the event of undesired reactions such as acute heart failure during therapy with β blockers It could likewise prove beneficial in cases of delayed atrioventricular conduction The elaboration of a simple test of coronary function with the aid of this preparation lies entirely within the bounds of possibility

Summary

The effects of single oral doses of 5 10 and 20 mg of a new cardioselective β stimulant preparation C 50 005/A Ba were tested and compared with the response to placebo in eight healthy volunteers (four aged 23 to 26 years and four aged 49 to 55 years) The compound induced a dose related increase in myocardial contractility (reduction of 17 to 24 msec in PEP) and in heart rate which was accelerated by 8 to 20 beats/minute by comparison with the placebo values The rise in systolic pressure observed in response to C 50 005/A Ba was both dose related and dependent on the age of the subjects in the younger group there was an increase of 16 to 31 mm Hg and in the older group an increase of 7 to 21 mm Hg A slight decrease in diastolic pressure was noted which was likewise more prominent in the younger subjects These changes were ascribed to a decrease due to aging in the responsiveness of the adrenergic β receptors to stimulation The effects of the compound set in quickly reached their maximum within 30 to 60 minutes and persisted for about 4 hours The only side effects observed were slight palpitations Depression of the ST segment was noted in one 55 year old subject and was interpreted as a manifestation of latent coronary disease In view of this finding it seems possible that the preparation could be used as a diagnostic agent for a simple test of coronary function Continuous E C G recordings over a period of 5¾ hours including three ergometer tests at submaximum effort showed that by comparison with placebo C 50 005/A Ba caused a slight increase in the frequency of isolated ventricular and supraventricular premature contractions and also in the incidence and intensity of sinus arrhythmias not due to respiration Essentially the same changes in cardiac rhythm were observed in four young volunteers during continuous E C G recordings over a period of 9 hours in response to the repeated administration of C 50 005/A Ba in a dosage of 15 mg three times a day on two consecutive days The differences from the corresponding placebo values were however not statistically significant

C 50 005/A Ba is thus an orally active cardio stimulant agent with a high degree of β_1 receptor selectivity and with only a very slight arrhythmogenic potential It is well tolerated and could afford beneficial effects in the treatment of heart failure or as a countermeasure in therapy with β blockers

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β receptors due to aging is a matter for speculation. This finding is concordant with the observations by Buhler and colleagues,[4] who reported that the extent to which the β receptors could be blocked *in hypertensive patients diminished with* age.

Another object of the present study was to ascertain whether the cardioselective β adrenergic receptor stimulant effect of C 50 005/A Ba is inevitably associated with an arrhythmogenic effect, such as the catecholamines are known to produce. Several authors[1,2,1,3] maintain that dobutamine has no such effect, but their conclusions are based on observations made in patients confined to bed. There have also been reports to the contrary. Loeb and associates[19] and Gunnar and co workers,[13] for instance, noted an increase in the frequency of ventricular extrasystoles during the infusion of dobutamine in patients with heart failure. The fact that ventricular and supraventricular extrasystoles can also occur in *persons free of any cardiac disorders makes it* extremely difficult to assess the arrhythmogenic potential of a drug. The published incidences of extrasystoles in *healthy* persons vary widely, in one study Engel and Burckhardt[10] recorded an incidence of 31 per cent, whereas Dietz and Kirchhoff[8] and Clarke and collaborators[7] quote figures up to 70 per cent and 72 per cent. McHenry and co workers[1] found a clear correlation between age and the occurrence of extrasystoles during maximum effort on a treadmill. In a later study the same authors[11] also observed that the individual reproducibility of effort induced ventricular extrasystoles in two consecutive tests was not more than 55 to 62 per cent depending on age; according to Jelinek and Lown[17] it was even below 50 per cent. Moreover, studies carried out by various investigators have shown that both the frequency and the type of arrhythmias occurring in clinically sound hearted persons differ greatly.[7,8,10] Conclusions as to the possible arrhythmogenic potential of a drug can only be reached if the E C G is recorded continuously over many hours. This was done in our study and in addition to pursuing their normal everyday activities after being treated with the substance, the subjects were also repeatedly subjected to a submaximum workload on the bicycle ergometer to increase the likelihood of arrhythmias becoming *manifest* by raising sympathetic tone. It was found that C 50 005/A Ba caused a slight statistically nonsignificant and non dose related in*crease in the frequency of supraventricular* and ventricular extrasystoles and an increase in the frequency and degree of marked sinus ar*rhythmias* which at the highest tested dose level of 20 mg was just barely significant in relation to the placebo values. Marked sinus arrhythmias such as we observed in seven of our eight subjects were seen by Engel and Burckhardt[10] in 34 per cent of their group of young subjects. Dietz and Kirchhoff[8] noted changes in the P wave with an abrupt, distinct slowing of heart rate in 55 per cent of their series of 30 to 40 year old subjects. These changes seem to arise in predominantly vagotonic phases, above all in relatively young asthenic individuals. The possibility that they may be due to depression of the sinus node pacemaker has been discussed.[8,7] The increase in sinus arrhythmias of this *type after* the administration of C 50 005/A Ba likewise seems to result from transient elevations of vagal tone caused by *a baroreceptor response to the increase in stroke* volume or blood pressure or both.[19] Like all other inotropic catecholamines the substance would *thus appear to have a certain though slight* arrhythmogenic potential. The clinical significance of this effect can only be assessed by further *careful investigation, preferably in patients with* heart disease.

The occurrence of a marked depression of the ST segment in one of the elder subjects *after the* administration of C 50 005/A Ba can be interpreted as a manifestation of latent coronary disease. It is not surprising that the substance should provoke this effect since it augments stroke volume and heart rate, and in the absence of vasodilatation also leads to a relative increase in afterload with a corresponding rise in the myocardial oxygen requirement. It is conceivable that a preparation of this type could be employed diagnostically in a simple test of cardiac function similar to that suggested by Rivier and colleagues[21] based on the infusion of isoprenaline. At all events this finding underlines the need for the utmost caution in the further evaluation of the compound if it is administered *to patients* with coronary disease.

Conclusions

On the basis of the available data preparation C 50 005/A Ba would appear to merit clinical trial in *all acute and chronic disorders associated*

Mechanism of antihypertensive effect of thiazide diuretics

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The thiazide diurectics have become established as the drugs of first choice in the treatment of hypertension Not only do they exert an independent antihypertensive effect but they also enhance the action of other antihypertensive drugs and prevent the development of resistance to various adrenergic blocking and vasodilator agents used for treating hypertensive patients

The mechanism of the antihypertensive effect of the thiazides has not been clarified Pharmacological textbooks [1] ascribe the antihypertensive action to two mechanisms as follows (1) depletion of extracellular fluid volume (ECF) including plasma volume accounting for the initial fall of blood pressure followed by (2) decreased peripheral vascular resistance due to a direct vasodilator action of the drug It is generally believed that the vasodilator action contributes importantly to the long term antihypertensive effect of these drugs [2] The presently accepted theory of the antihypertensive action of the thiazides therefore defines two entirely separate mechanisms a diuretic and a vasodilator action Furthermore they are said to act primarily in sequence rather than together Such a dual theory however must be regarded with suspicion because (1) it is unusual for any drug to exert its therapeutic effect via one mode of action initially and via an entirely different mechanism later on and (2) a direct vasodilator effect of the thiazides has never been convincingly demonstrated

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In the present investigation the mode of action of the thiazides has again been investigated by recording both the short and long term effects of hydrochlorothiazide Among the hemodynamic parameters investigated are cardiac output plasma volume and ECF Using these data as well as previous reports in the literature a unitary rather than the present dual theory of the mode of action of the thiazides will be presented

Methods

Thirteen patients with essential hypertension of mild to moderate severity who were attending the Hypertension Clinic of the Veterans Administration Hospital consented to participate in the study after being fully informed of its design and purposes The patients either were previously untreated or were receiving thiazide diuretics without other drug treatment Prior to the control determinations the latter patients were placed on placebos for a 2 to 3 week period Pill counts were carried out throughout the trial as a test of compliance One patient dropped out while another was noncompliant as judged by the pill counts Both were dropped from the study

The patients were studied on four occasions as follows before treatment 48 hours after beginning treatment with hydrochlorothiazide 50 mg twice daily to determine acute effects of the drug and 6 weeks as well as 8 weeks after beginning treatment with hydrochlorothiazide for assessing long term effects

During test days patients came to the laboratory in the fasting state An 18 gauge Teflon catheter was inserted into an antecubital vein to facilitate blood sampling Plasma volume and extracellular fluid measurements were determined in eight patients by the method of Gregersen and Stewart [3] adapted for use with the

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Table I Hemodynamic changes from control at 48 hours 6 weeks and 8 weeks after beginning treatment with hydrochlorothiazide

Parameter	No of cases	Control	During treatment					
			48 Hours		6 Weeks		8 Weeks	
		Mean	Mean	P*	Mean	P*	Mean	P*
Body weight (lbs)	11	201	197	< 005	197	< 05	196	< 01
Hematocrit (%)	11	40 4	43 1	< 005	42 6	< 0005	42 7	< 0005
Plasma volume (L)	8	3 69	3 23	< 005	3 33	< 005	3 47	NS
Extracellular fluid volume (L)	8	20 4	18 0	< 005	16 4	< 0005	15 4	< 005
Systolic blood pressure (mm Hg)	11	153	135	< 01	130	< 01	131	< 005
Diastolic blood pressure (mm Hg)	11	103	95	< 05	92	< 025	91	< 01
Heart rate (per min)	11	76	79	NS	78	NS	77	NS
Cardiac output (L /min)	11	6 4	5 4	< 025	6 4	NS	6 0	NS
Total peripheral resistance (Dynes cm /sec)	11	1479	1716	08	1356	NS	1393	NS

Change from control using 1 tailed test.

Table II Simultaneous determination of cardiac output by the Cardiogreen dye and CO_2 rebreathing methods

Patient No	Control period				After 8 weeks of thiazide treatment			
	Cardiac output CO (L /min)	Cardiac output Dye (L /min)	Mean arterial pressure† (mm Hg)	Total peripheral resistance (Dynes cm sec)	Cardiac output CO (L /min)	Cardiac output Dye (L /min)	Mean arterial pressure (mm Hg)	Total peripheral resistance (Dynes-cm sec)
6	7 85	6 83	115	1346	6 80	8.3	110	1294
8	7 39	6 37	151	1897	4 98	5 83	95	1303
9	8 06	6 71	113	1346	6 02	6.15	105	1482
10	5 91	4 90	133	2171	6 90	6 45	123	1425
11	7 02	7 19	9[illegible]	1023	6 27	6 01	87	1158
Mean	7 11	6 40	121	1557	6 50	6.25	104	135[illegible]
S D	0 11	0 89	22	466	0 13	0 38	14	150

Dye outputs used to calculate total peripheral resistance
†Direct intra-arterial recording of blood pressure

measured directly using a Statham strain gauge After injecting rapidly 5 mg Cardiogreen in one ml distilled water into the central vein using a flush of 5 ml saline blood was withdrawn from the brachial artery through a Gilford densitometer using a motor driven withdrawal syringe The resulting dye-concentration curve was recorded on a Hewlett Packard oscillographic recorder Because of the more invasive nature of the procedure three such dye curves were recorded only during the control period and again at 8 weeks following initiation of treatment It was not considered necessary to determine the acute effects of thiazides on cardiac output with the dye technique because such early effects as were determined by the dye dilution method have already been well defined[5,8] The dye dilution method was used primarily to confirm the results obtained with the noninvasive CO_2 method on the effects of long term treatment with the thiazides

Results

Cardiac output blood pressure total peripheral resistance and heart rate Cardiac output as determined by the CO_2 rebreathing method fell significantly ($P < 05$) from a mean value of 6 4 L per minute during the control period to 5 4 L per minute 48 hours after beginning hydrochlorothiazide (Table I Fig 1) However 6 and 8 weeks after beginning treatment with hydrochlorothiazide cardiac output rose to or toward the

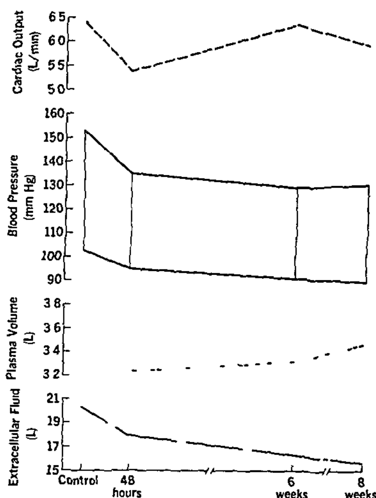


Fig 1 Mean changes in cardiac output blood pressure plasma volume and extracellular fluid volume (thiocyanate space) before as well as 48 hours 6 weeks and 8 weeks after treatment with hydrochlorothiazide

spectrophotometer The procedures were carried out after the patients had remained continuously in the recumbent position for at least 30 minutes After drawing control samples of blood 22 5 mg of Evans Blue dye in 5 ml of distilled water and 18 ml of 5 per cent sodium thiocyanate were injected into an antecubital vein using calibrated syringes Blood samples were drawn from a vein in the opposite arm for plasma volume determination at 10 15, and 20 minutes after the injection of Evans Blue dye The concentrations at these times were plotted on semilog paper and a best fit line was extrapolated back to zero time The latter concentration was taken as the value present after mixing and before any disappearance of the dye

Blood samples were drawn for thiocyanate determinations at 2 hours following injection as well as 10 minutes later Thiocyanate concentration of the second sample was required to agree within 5 per cent of the first The average concentration of these two samples corrected for the plasma blank was used to determine the thiocyanate space[3] While this method only approximates the true extracellular fluid volume since the thiocyanate ion enters red cells and other compartments prior experience indicated that this method is reliable for measuring *changes* in the ECF[4]

Cardiac outputs were determined by the CO rebreathing method alone in six patients and by the CO_2 rebreathing method and the dye dilution methods in five patients Cardiac output was determined by the CO_2 rebreathing method *before the administration of hydrochlorothiazide* and 48 hours 6 weeks and 8 weeks after initiating treatment with the drug After resting in the supine position for at least ten minutes the blood pressure was recorded by the same observer throughout, using the standard auscultatory method The fifth phase of the Korotkoff sounds were used as the indication of diastolic blood pressure The blood pressure was recorded before and after each determination of cardiac output and the results were averaged The initial determinations of blood pressure and cardiac output were discarded in order to accustom the patient to the procedure prior to the collection of data Cardiac output also was determined by the dye method in five of the patients before beginning treatment with hydrochlorothiazide and 8 weeks after beginning treatment The significance of differences after as compared to before treatment was determined using Student s t test

The technique of Franciosa and associates[5] was used for estimating cardiac output by the CO_2 rebreathing method Their technique was modified slightly with respect to the point at which CO_2 is measured in the expired air Rather than using forced expiration which in our hands frequently lead to an overestimate of alveolar CO_2 we recorded the CO_2 concentration in expired air during normal or deep respiration at a point where the expired volume approximated 400 ml The CO_2 concentration and the respiratory volume were recorded continuously and simultaneously The 400 ml point was chosen because it well exceeded the dead space volume of 150 to 250 ml but was not so large as to reflect the *CO* concentration in underventilated alveoli such as we had experienced using forced expiration

For the dye dilution method a polyethylene catheter was inserted into an antecubital vein and was threaded into a central vein A Teflon catheter was then inserted via a needle into the brachial artery Mean arterial blood pressure was

reflex increase in heart rate and cardiac output similar to that seen with other vasodilator drugs such as hydralazine or amyl nitrite Acute administration of the thiazides however is associated with the opposite hemodynamic effects that is with an increase in total peripheral resistance and a fall in cardiac output [7, 8] Also the initial observation[14] that hypotension preceded the diuresis has not been confirmed as three other investigations concluded that the fall in blood pressure occurred only after an effective diuresis [6-] Furthermore a direct vasodilator effect of the thiazide diuretics has not been convincingly demonstrated

The vasodilator theory of the action of the thiazides has been further questioned by the observation that other diuretics such as parenteral mercurials and ethacrynic acid [9] also exhibit an antihypertensive effect These drugs have in common volume depleting effects rather than vasodilator properties Also the reduction of blood pressure occurring in patients receiving the low sodium rice diet is associated with a significant reduction in ECF [2] All of the above antihypertensive procedures decrease ECF suggesting that it is the latter which is causally implicated in the reduction of blood pressure in both the acute and chronic responses

Volume depletion following acute administration of the thiazides has been documented by many investigators [6, 2, 2] Patients undergoing continuous treatment with thiazides lose about 2 L of ECF and about 300 to 400 ml of plasma volume during the first 72 hours of treatment After this time there is no additional volume depletion However the reduction in ECF which occurs during the first 72 hours is maintained Patients receiving diets severely restricted in sodium show quantitatively similar reductions averaging 10 per cent of the ECF and 15 per cent of the plasma volume [2]

The importance of reduced volume is again indicated by observations that the antihypertensive effects of combined treatment with thiazide diuretics and adrenergic blocking agents can be reversed in many patients by re expanding the plasma volume with salt free dextran [6, 1] However in patients treated with thiazides without adrenergic blocking agents dextran will only occasionally but not usually restore the hypertension Nevertheless oral ingestion of 20 to 30 Gm salt which is sufficient to re-expand total ECF despite the administration of thiazides does restore the hypertension even during long term treatment [2, 24] This suggests that re expansion of total ECF rather than plasma volume alone is required to overcome completely the antihypertensive effects of the thiazides

Three possible mechanisms can be postulated to explain how thiazide induced reduction of ECF lowers blood pressure Firstly volume depletion may blunt environmental pressor stimuli while at the same time enhancing depressor influences For example patients receiving ganglion blocking agents often exhibit marked hypotensive responses with only small reduction of blood volume [27] It has further been observed that following either thiazide or mercurial induced diuresis the depressor responses to infused trimethaphan are increased [25] Also expansion of ECF in rats results in an enchanced pressor response to angiotensin whereas ECF depletion has the opposite effect [29] Volume depletion therefore seems to dampen pressor reactions and increase depressor responses the combined effects of which could result in a reduction of average blood pressure While this theory is attractive it does not explain the rise in cardiac output toward control values and fall in total peripheral resistance which occurs with long term treatment

The second possible mechanism by which volume depletion may lower blood pressure is via the baroreceptor reflexes It has been noted clinically that elderly patients often exhibit an enhanced hypotensive response to the thiazide diuretics requiring reduction of dosage often to quite small amounts On the other hand young normal adults do not show an antihypertensive effect with the thiazide diuretics although their heart rates increase significantly consistent with an active barorreceptor response to the lower blood pressure associated with the volume depletion [23] Elderly normal subjects however do show a fall of blood pressure with the thiazide diuretics [30]

Baroreceptor reflex responses depend upon the compliance of the aorta and carotid artery These vessels become less distensible as a result of structural changes induced by aging or by hypertension Homeostatic circulatory adjustment to pressor stimuli are poorly moderated in long standing chronic hypertension [3] While the evidence is incomplete it is consistent with the

pretreatment values and was then insignificantly different from the pretreatment control level.

Cardiac output determined by the dye method in five patients agreed reasonably well with the cardiac output determined by the CO_2 rebreathing method (Table II). The correlation coefficient comparing both methods was r = 0.84 ($P < .05$) during the control period and r = 0.97 ($P < .005$) after 8 weeks of treatment. After 8 weeks the mean change in cardiac output from pretreatment control was −0.2 L and −0.6 L for the dye and CO_2 rebreathing methods, respectively. Neither change was significant.

By contrast to the initial fall and later return of cardiac output, the blood pressure fell early and remained reduced (Table I, Fig. 1). The average control blood pressure of 153/103 fell to 135/95 mm Hg after 48 hours ($P < .05$). After 6 and 8 weeks of treatment the blood pressure was even lower, averaging 130/92 and 131/91 mm Hg at 6 and 8 weeks, respectively ($P < .025$).

Total peripheral resistance increased initially from a mean of 1479 dynes cm^{-5} sec in the control period to 1716 dynes cm^{-5} sec 48 hours after beginning hydrochlorothiazide. The change was of borderline significance ($P = .09$). After 6 and 8 weeks, total peripheral resistance decreased slightly but not significantly below the control level, the mean values being 1356 and 1393 dynes cm^{-5} per second respectively at the 6 and 8 week post treatment periods.

Heart rate did not change significantly throughout the treatment period. The mean value for heart rate rose insignificantly from 76 per minute in the pretreatment period to 79 per minute at 48 hours after beginning treatment. The mean values for heart rate at 6 and 8 weeks after beginning treatment remained within the range of these values.

Extracellular fluid volume, plasma volume, hematocrit, and body weight. ECF measured in eight patients by the thiocyanate method fell significantly and remained reduced throughout the period of observation (Table I). From a mean control value of 20.4 L the ECF decreased 12 per cent to 18.0 L at 48 hours after beginning hydrochlorothiazide. The reductions in ECF were even greater at 6 and 8 weeks, averaging 20 and 24 per cent, respectively, below the control mean.

Plasma volume decreased from a mean of 3.69 L in the control period to 3.23 L 48 hours after beginning treatment with hydrochlorothiazide. The decrease averaged 13 per cent and was highly significant ($P < .005$). Plasma volume remained reduced at 6 and 8 weeks after treatment with hydrochlorothiazides, although the change attained statistical significance only at the 6 weeks interval.

Reflecting the decrease in plasma volume the hematocrit rose and remained significantly above the control mean throughout the 8 week period of treatment. The mean value in the control period was 40.4 and this rose to 43.1 after 48 hours of treatment, an increase of 7 per cent. The mean values at 6 and 8 weeks of treatment were essentially the same as at 48 hours (Table I).

Body weights decreased at 48 hours after treatment and remained significantly below the control for the remainder of the period of observation. The average loss of weight was 4 pounds or 1.8 kilograms at 48 hours, increasing to 5 and 6 pounds (2.3 and 2.7 kilograms), respectively, at 6 and 8 weeks after beginning treatment.

Discussion

Three principal hypotheses have been advanced to explain the antihypertensive effects of the thiazide diuretics. The first two hypotheses are concerned with sodium depletion, of which one ascribes the fall in blood pressure to a reduction in total ECF and the other to a loss of sodium from the arterial walls. The latter hypothesis probably can be discarded because studies from three independent sources found no evidence that thiazides affect the sodium content of either large or small arteries in rats.[9-11] The third and most popular hypothesis is that the hypotensive effect, at least during chronic treatment, is due to a direct vasodilator effect of these drugs.[1,2]

Hollander, Chobanian, and Wilkins[12] found no reduction in extracellular fluid volume after one to six months of treatment with chlorothiazide. On the basis of this and other data, they concluded that the antihypertensive effect was not due solely to sodium depletion. Their conclusion gained support from the observation that the chemically related compound diazoxide[13] is a vasodilator antihypertensive compound which produces sodium retention rather than diuresis.[14,15] According to Rowe and colleagues[15] acute administration of diazoxide is associated with a considerable decrease in total peripheral resistance in hypertensive patients and with a

reflex increase in heart rate and cardiac output similar to that seen with other vasodilator drugs such as hydralazine or amyl nitrite Acute administration of the thiazides however is associated with the opposite hemodynamic effects that is with an increase in total peripheral resistance and a fall in cardiac output[7, 8] Also the initial observation that hypotension preceded the diuresis has not been confirmed as three other investigations concluded that the fall in blood pressure occurred only after an effective diuresis[4, 5] Furthermore a direct vasodilator effect of the thiazide diuretics has not been convincingly demonstrated

The vasodilator theory of the action of the thiazides has been further questioned by the observation that other diuretics such as parenteral mercurials[1] and ethacrynic acid[1] also exhibit an antihypertensive effect These drugs have in common volume depleting effects rather than vasodilator properties Also the reduction of blood pressure occurring in patients receiving the low sodium rice diet is associated with a significant reduction in FCF[0, 2] All of the above antihypertensive procedures decrease ECF suggesting that it is the latter which is causally implicated in the reduction of blood pressure in both the acute and chronic responses

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concept that the antihypertensive effect of the thiazide diurectics, at least in patients with *noncompliant* arteries, could be due in part to an inadequate baroreceptor compensation for the volume depletion and reduced cardiac output

The third, and we believe most likely mechanism, for explaining the hemodynamic changes seen with the thiazide diuretics involves feedback autoregulatory responses to a prolonged reduction in cardiac output as originally suggested by Tobian [3, 33] Such feedback autoregulatory systems have been postulated to explain the rise of blood pressure which occurs in certain types of experimental hypertension In experimental renovascular hypertension[34] or in the hypertension caused by reduction in renal mass plus salt loading [35] or in the hypertension induced by excess licorice ingestion in man [36] the following sequence of events was observed during the development of the hypertension (1) salt and water retention, leading to (2) expansion of the ECF and plasma volume resulting in (3) increased venous pressure and venous return to the heart followed by (4) increased cardiac output, (5) rise in blood pressure leading to (6) increase in urine volume preventing further rise in ECF followed by (7) gradual elevation of total peripheral vascular resistance occurring over a period of weeks It was postulated that the rise in total peripheral resistance was due to autoregulation in response to the elevated peripheral blood flows which were in excess of local metabolic needs because of the increased cardiac output At the same time, there was (8) reduction of the elevated cardiac output toward normal because of the elevated afterload resulting from the increase in total peripheral resistance Thus the hypertension which was initiated by an expansion of ECF and resulting increase in cardiac output evolved after approximately one month into a hypertension characterized by an elevated total peripheral resistance and normal cardiac output

Tobian[3, 33] has postulated that thiazides and related diuretics induce reverse autoregulation which leads to a decrease in total peripheral resistance Thus reduction in ECF caused by thiazides produce initially a fall in central venous pressure venous return and cardiac output At first, this is associated with an increased total peripheral resistance However with continued treatment and maintained reduction in cardiac output and total blood flow, autoregulation occurs gradually over a period of weeks leading to a decline in total peripheral resistance Finally, we suggest that the resulting fall in afterload permits a rise in cardiac output toward normal This sequence of hemodynamic events is the same as that actually observed during the early and late phases of continuous treatment with the thiazides and they all follow from a single hemodynamic effect of the thiazides which is a sustained reduction in ECF No direct vasodilator action of the thiazides need to be postulated as the early fall and later return of cardiac output to normal and the early rise and later fall in total peripheral resistance can both be explained by the reduction in ECF alone

Most pharmacological textbooks differentiate between the short term and long term effects of thiazides [1, 2] According to these texts the short term antihypertensive effect is due primarily to volume depletion while the long term effect is ascribed to a vasodilator action of the thiazides The principal evidence for such a dual mechanism of action is the report of Conway and Lauwers,[37] which indicates that plasma volume and ECF fall initially but then return to essentially control values after one month of continuous treatment with chlorothiazide These investigators concluded that decreased ECF could not have an influence on the long term antihypertensive effect of the thiazides

Other investigators, however, have not corroborated the observations of Conway and Lauwers Wilson and Freis[4] found a significant reduction of ECF after six months of continuous treatment with chlorothiazide Plasma volume also was reduced at six months although not significantly However, at 12 months plasma volume was significantly lower than control More recently, other investigators also found a continued reduction of plasma volume and ECF during long term treatment with thiazides [38, 39] Furthermore following withdrawal of long term treatment there was a prompt and significant rise of plasma volume ECF and blood pressure providing further evidence that the thiazides continue to maintain their volume reducing effect during chronic administration [4, 39]

Conway and Lauwers[37] also observed that while cardiac output falls initially after administration of thiazide it returns to normal after one month The latter observation has been confirmed in the present study and by Lund-Johan

sen[40] During the first few days of treatment cardiac output is reduced and total peripheral resistance is increased[6-8] However after a month or more of treatment cardiac output rises to or toward control values while total peripheral resistance falls These changes can be explained by reverse autoregulation without invoking a separate vasodilator effect of the thiazide diuretics

Autoregulation may not be limited to the thiazides alone Other antihypertensive agents also induce differing hemodynamic effects during acute and chronic administration Guanethidine an adrenergic blocking agent causes an initial fall in cardiac output but with long term treatment cardiac output rises gradually back toward normal[1] Hydralazine a vasodilator agent initially increases cardiac output but the latter returns toward normal during chronic treatment[4] These observations suggest that autoregulatory responses which return the cardiac output toward normal often occur during long term administration of antihypertensive agents

Summary

Hemodynamic studies were carried out before and during 8 weeks of treatment with hydrochlorothiazide 50 mg twice daily in 11 hypertensive patients Forty eight hours after beginning treatment there was a significant reduction in blood pressure cardiac output plasma volume and extracellular fluid volume (thiocyanate space) while total peripheral resistance increased After 6 and 8 weeks of treatment the blood pressure and the plasma and extracellular volumes remained reduced However total peripheral resistance fell while cardiac output rose to control levels These results were consistent with the reverse autoregulation theory of the action of the thiazides as proposed by Tobian The present findings as well as other clinical and experimental evidence discussed below makes it appear unlikely that the thiazides have an important direct vasodilator effect

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concept that the antihypertensive effect of the thiazide diurectics, at least in patients with noncompliant arteries, could be due in part to an inadequate baroreceptor compensation for the *volume depletion and reduced* cardiac output

The third and we believe most likely mechanism, for explaining the hemodynamic changes seen with the thiazide diuretics involves feedback autoregulatory responses to a prolonged reduction in cardiac output as originally suggested by Tobian [32, 33] Such feedback autoregulatory systems have been postulated to explain the rise of blood pressure which *occurs in certain types of* experimental hypertension In experimental renovascular hypertension[34] or in the hypertension *caused* by reduction in renal mass plus salt loading,[35] or in the hypertension induced by excess licorice ingestion in man [36] the following sequence of events was observed during the development of the hypertension (1) salt and water retention, leading to (2) expansion of the ECF and plasma volume resulting in (3) increased venous pressure and venous return to the heart, *followed by (4) increased cardiac output (5) rise* in blood pressure leading to (6) increase in urine volume preventing further rise in ECF followed by (7) gradual elevation of total peripheral vascular resistance occurring over a period of weeks It was postulated that the rise in total peripheral resistance was due to autoregulation in response to the elevated peripheral blood flows which were in excess of local metabolic needs because of the increased cardiac output At the same time, there was (8) reduction of the elevated *cardiac output toward normal because of the* elevated afterload resulting from the increase in total peripheral resistance Thus the hypertension which was initiated by an expansion of ECF and resulting increase in cardiac output evolved after approximately one month into a hypertension characterized by an elevated total peripheral resistance and normal cardiac output

Tobian[32, 33] has postulated that thiazides and related diuretics induce reverse autoregulation which leads to a decrease in total peripheral resistance Thus reduction in ECF caused by thiazides produce initially a fall in central venous pressure, venous return, and cardiac output At *first,* this is associated with an increased total peripheral resistance However, with continued treatment and maintained reduction in cardiac output and *total blood flow,* autoregulation occurs gradually over a period of weeks leading to *a decline in total* peripheral resistance Finally we suggest that the resulting fall in afterload permits a rise in cardiac output toward normal This sequence of hemodynamic events is the same as that actually observed during the early and late phases of continuous treatment with the thiazides and they all follow from a single hemodynamic effect of the thiazides which is a sustained reduction in ECF *No direct vasodilator* action of the thiazides need to be postulated as the early fall and later return of cardiac output to *normal and the early rise and later fall* in total peripheral resistance can both be explained by the reduction in ECF alone

Most pharmacological textbooks differentiate between the short term and long term effects of thiazides [1, 2] According to these texts the short term antihypertensive effect is due primarily to volume depletion while the long term effect is ascribed to a vasodilator action of the thiazides The principal evidence for such a dual mechanism of action is the report of Conway and Lauwers [37] *which indicates that plasma volume and ECF* fall initially but then return to essentially control values after one month of continuous treatment with chlorothiazide These investigators concluded that decreased ECF could not have an influence on the long term antihypertensive effect of the thiazides

Other investigators however have not corroborated the observations of Conway and Lauwers Wilson and Freis[4] found a significant reduction of ECF after six months of continuous treatment with chlorothiazide Plasma volume also was reduced at six months although not significantly However, at 12 months plasma volume was signif*icantly lower than control* More recently, other investigators also found a continued reduction of plasma volume and ECF during long term treatment with thiazides [38, 39] *Furthermore* following withdrawal of long term treatment there was a prompt and significant rise of plasma volume ECF and blood pressure *providing further* evidence that the thiazides continue to maintain their volume reducing effect during chronic administration [4, 35]

Conway and Lauwers[37] also observed that while cardiac output falls initially after administration of thiazide it returns to normal after one month The latter observation has been confirmed in the present study and by Lund-Johan

Changes in components of kinin system and hemodynamics in acute myocardial infarction

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The mortality rate following acute myocardial infarction has been recently reduced but remains high in patients who develop cardiogenic shock Since the incidence of pump failure appears to be related to infarct size [2] recent investigations have emphasized reduction of infarction by administration of various pharmacologic or mechanical interventions However the significance of the role of metabolic and neurohumoral factors in acute ischemic states and in the development of cardiogenic shock remains to be elucidated

Because of its potent pain producing and hypotensive actions kinin has been proposed as one of the factors contributing to chest pain and development of shock in patients with angina pectoris or acute myocardial infarction [3-7] These hypotheses were largely based on measurements of kininogen the inactive precursor of kinin yet validation of the kinin mechanisms during myocardial ischemia requires determination of sequential alterations in kinin itself along with simultaneous hemodynamic and metabolic measurements

In our previous studies in dogs with coronary occlusion we observed a marked increase in coronary sinus blood kinin levels accompanied by a significant decrease in myocardial contractility [8] This might indicate that the kinin release secondary to acute myocardial ischemia could be a factor in the development of cardiogenic shock The purpose of the present study was to investigate alterations in kinin and hemodynamics in two subsets of patients with acute myocardial infarction Subset A consisted of patients who survived more than 1 month and subset B consisted of patients who died of pump failure within 3 days of acute myocardial infarction

Materials and methods

The study included 23 patients who had been hospitalized in our clinic with acute myocardial infarction Of these 16 survived more than 1 month s observation period The remaining seven patients died of shock or congestive heart failure within 3 days after onset of the infarction Sites of infarction in the 16 survivors were anteroseptal in nine anterolateral in two anteroposterior in one posterior in three and lateral infarction in one case Except for occasional premature ventricular contractions no major complications were observed in these patients Of the seven non surviving patients four died of cardiogenic shock (three anteroseptal and one lateral infarction) and three of congestive heart failure (one anterolateral and two posterior infarction) Sequential blood samples were taken from the cubital vein 1 2 3 4 5 6 7 10 15 20 25 and 30 days after the heart attack in the survivors and up to the time of death in the non survivors Plasma kininogen

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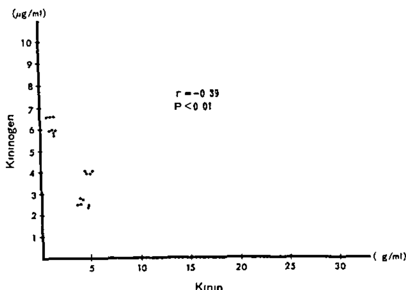


Fig 3 Relationship between kininogen and kinin levels in the same blood samples obtained from the cubital vein in surviving patients (N = 143)

the onset of infarction Three out of the nine cases observed more than 15 days returned to normal but kinin levels remained elevated in six throughout 30 days postinfarction

Relationship between kininogen and kinin The relationship between kininogen and kinin measurements was plotted in Fig 3 and a weak though significant correlation was obtained ($r = -0.39$ $p < 0.01$) This might indicate that kinin was activated in blood from kininogen through the action of kininogenases

Correlation between blood pressure kininogen and kinin Fig 4 illustrates changes in blood pressure kininogen and kinin in the 16 surviving patients The preinfarction blood pressure obtained in the outpatient clinic served as baseline control and subsequent alterations are expressed as per cent change The blood pressure decreased on the first day of infarction by 20 per cent and dropped further to a maximum change of 28 per cent on the second day Subsequently blood pressure recovered slightly but remained below control throughout the 30 day observation period The correlations between lowering of blood pressure and those of kininogen and kinin levels within the first 10 days of infarction were weak but significant ($r = -0.46$ $p < 0.05$ for kininogen and $r = 0.30$ $p < 0.05$ for kinin) Thus some causal relationship might exist between the lowering of blood pressure and increased levels of kinin substances during the early stage of acute myocardial infarction

Cardiac output total peripheral resistance and circulation time As shown by the solid columns in each panel of Fig 5 normal baseline ranges for cardiac output total peripheral resistance and circulation time were 4 4 ± 0 5 L /minute 1746 ± 169 dyne sec /cm and 10 6 ± 0 4 sec. respectively Cardiac output dropped on the first day of acute myocardial infarction (by 36 per cent) and tended to recover during the subsequent 5 days Total peripheral resistance was elevated on the first day by 65 per cent then tended to decrease reaching a minimal value on the fourth day from the infarction After the seventh day total peripheral resistance was almost back to the normal level Circulation time increased on the first day (by 39 per cent) and reached a maximum on the second day (14 7 ± 1 3 sec) Thereafter it tended to gradually recover

Correlation between kinin system substances and hemodynamics Table I summarized the correlations between kininogen and kinin changes on the one hand and alterations in hemodynamics including blood pressure cardiac output total peripheral resistance and circulation time on the other Significant negative correlations were noted between kininogen and lowering of blood pressure ($r = -0.46$ $p < 0.05$) as well as

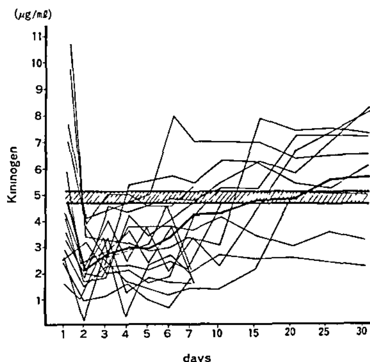


Fig 1 Changes in kininogen levels in cubital vein blood in 16 surviving patients Mean values are shown by a thick line and individual patients are represented by thin lines A cross hatched zone indicates normal range (mean ± S E M)

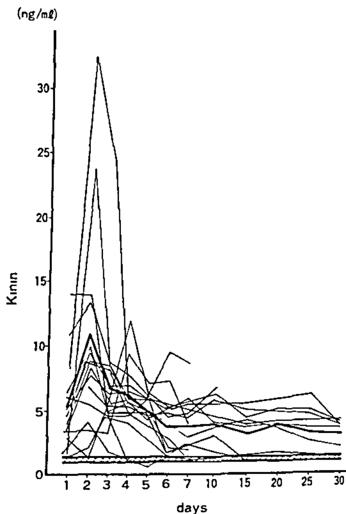


Fig 2 Changes in kinin levels in cubital vein blood in 16 surviving patients Mean values are shown by a thick line and individual patients are represented by thin lines A cross hatched zone indicates normal range (mean ± S E M)

and kinin were extracted from the blood samples according to the methods of Brocklehurst and Zeitlin[10] and Abe and associates,[11] respectively, and bioassayed using the perfused guinea pig ileum Five healthy subjects were also used to determine control levels of the kinin system substances over a period of 7 days

Simultaneous with blood sampling blood pressure and heart rate were measured and cardiac output as well as circulation time (forearm to ear) was obtained by means of the dye dilution technique (Waters instruments Inc Model PR 52) Total peripheral vascular resistance was calculated Data were expressed as mean ± standard error of the mean (SEM) and statistical analysis of the data was performed by the Student t test

Results

I Surviving patients (16 cases)

Kininogen Fig 1 illustrates changes in kininogen levels in cubital vein blood samples during the postinfarction observation period The mean values are shown by a thick line whereas individual patients are represented by thin lines For comparison, the baseline value of 5 3 ± 0 3 μg/ml , established in five normal subjects is also indicated by a cross hatched zone It is seen that two thirds of the patients exhibited a reduced kininogen level on the first day A further decrease was observed on the second day (2 4 ± 0 3 μg/ml) Thereafter kininogen values tended to recover, reaching near normal levels 10 or 15 days from the onset of the infarction Nine of the 16 patients were followed up to 30 days and of these six exceeded the normal kininogen level while two remained below normal

Kinin Alterations in the kinin levels in cubital vein blood sampled in surviving patients are shown in Fig 2 Baseline kinin values from five normal individuals were established as 1 2 ± 0 1 ng /ml and are indicated by the cross hatched area Except for one all patients exhibited kinin elevation on the first day after the infarction followed by a further significant increase on the second day to 10 1 ± 2 0 ng /ml Subsequently kinin levels tended to decrease but the mean value remained above normal even 30 days after

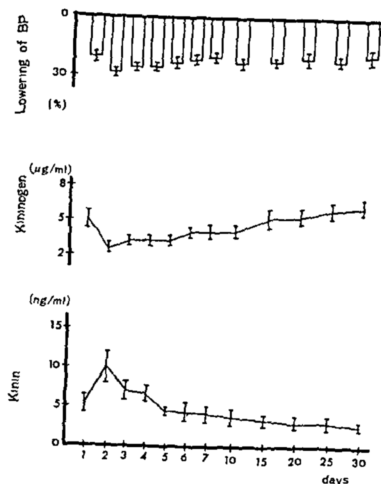


Fig 4 Changes in blood pressure kininogen and kinin in the 16 surviving patients (mean ± S E M)

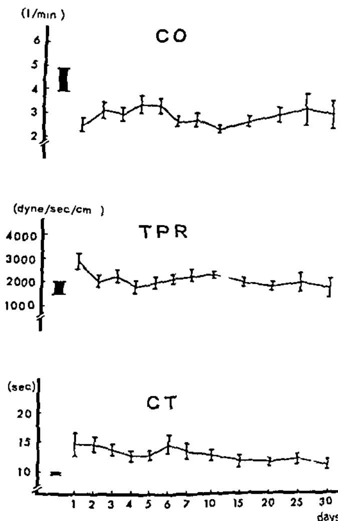


Fig 5 Changes in cardiac output (*top*) total peripheral resistance (*middle*) and circulation time (*bottom*) in nine surviving patients (mean ± S E M) *Solid columns* in each panel indicate normal ranges (mean ± S E M)

Table I Correlations between changes in kinin system substances and alterations in hemodynamics

	Kininogen	*Kinin*
Lowering blood pressure	−0 46	0 30
Cardiac output	−0 15	0 05
Total peripheral resistance	0 35*	−0 41 *
Circulation time (arm–ear)	−0 41	0 59*

p ~ 0 05
p < 0 01

circulation time (r = −0 41, p < 0 01) Significant positive correlation was also seen between kininogen and total peripheral resistance (r = 0 35, p < 0 05) There were significant correlations of r = 0 30 (p < 0 05) between kinin and lowering of blood pressure and of r = −0 41 (p < 0 01) between kinin and total peripheral resistance Significant positive correlation was also observed between kinin and circulation time (r = 0 59 p < 0 01)

These data suggest that kinin system substances activated after the onset of myocardial infarction might play a role in dilating peripheral vessels and thus prolonging the circulation time

II Changes in kinin system substances in non survivors Of the seven patients who failed to survive more than 3 days after the onset of acute myocardial infarction, two died on the first day, one on the second day and four on the third day Four out of these seven patients died of cardiogenic shock and three of congestive heart failure

Blood samples were taken more than once a day Sequential determinations of kininogen and kinin blood levels from the onset of infarction until death are indicated in Fig 6 For comparison kininogen and kinin levels measured within 3 days after the onset in the survivors are also shown

Kininogen levels in the non survivors were 4 0 ± 0 3 μg/ml, which was lower than in normal

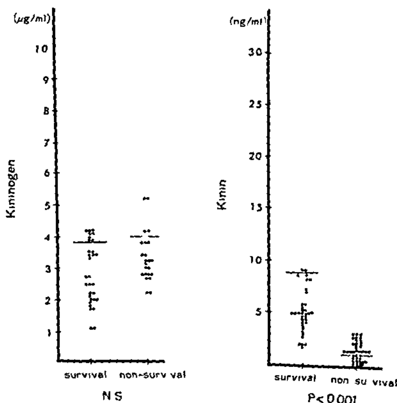


Fig 6 Blood kininogen (*left panel*) and kinin (*right panel*) levels in surviving as well as non surviving patients within 3 days from the onset

controls but no significant difference was noted when compared to surviving patients (3 8 ± 0 3 μg/ml) On the other hand there was a dramatic difference in kinin levels between survivors and non survivors Thus in survivors the mean kinin level within 3 days of infarction was 8 7 ± 0 9 ng / ml significantly higher than normal In contrast kinin levels in the non survivors remained within normal limits (1 0 ± 0 1 ng./ml) Thus while a reduction in kininogen was associated with increased kinin levels in survivors no increase in kinin was observed in the non survivors in spite of decreased kininogen levels

Discussion

It has been proposed that plasma kinin plays an important role in shock states secondary to hemorrhage endotoxin[2] anaphylaxis[11] pancreatitis burns and trauma[11] Kinin has also been implicated in cardiogenic shock and is thought to be an important factor in death from acute myocardial infarction Our previous study of coronary artery ligation in dogs[4] demonstrated that kinin levels in coronary sinus blood increased following coronary occlusion and correlated with decreased myocardial contractility and elevated left ventricular end diastolic pressure When dogs were pretreated with aprotinin (Trasylol an inhibitor of the kinin releasing enzyme) the post ligation increase in kinin and associated hemodynamic alterations were inhibited We surmised that release of myocardial kinin following coronary artery ligation might contribute a negative inotropic action which could be a factor in the development of cardiogenic shock However these observations were limited to very short term experiments In this study, we investigated changes in kinin system substances in patients with acute myocardial infarction An unexpected observation of this study was that kinin did not increase in patients who died of pump failure although kininogen levels decreased There was no correlation in these patients between the kinin measurements and hemodynamic indices such as blood pressure and cardiac output (data not shown) On the other hand surviving patients exhibited a decrease in kininogen as well as an increase in kinin both of

which were significantly related to a lowering of blood pressure decreased total peripheral resistance, and prolongation of *circulation time* during the early stage of the infarction These observations indicated that kinin system substances might not play a major role in the *pathogenesis of shock or heart failure* following acute myocardial infarction

We considered possible reasons for the observed differences in kininogen and kinin changes between surviving and non surviving patients The reasons why no kinin elevation was found in non survivors, in spite of decreased kininogen, might be attributed to the fact that (1) kinin released in the ischemic myocardium may not be adequately washed out from the ischemic zone because of severe regional hypoperfusion, (2) the released kinin may be rapidly inactivated by the lung or through potent kininase activity in the circulating blood, (3) a low kininogen level in non survivors may be due to impairment of its synthesis by the liver, (4) there was interaction with drugs used for treatment of the shock state As to the first theory low kininogen and unchanged kinin levels were observed even before perfusion pressure had been above the shock level in non survivors and no correlation was obtained between kinin system substances and blood pressure Thus this cannot be considered As to the third possibility liver damage and/or hypoproteinemia were not always seen in these patients Thus this hypothesis appears unreasonable Regarding the fourth proposition, norepinephrine *dopamine digitalis furosemide or steroids* were administered to patients to maintain the blood pressure but these changes in blood kinin system substances were also observed in samples taken *before drug treatment* We *therefore* believe that the low kininogen and normal kinin levels found in non survivors might be due to the high kininase activity in the lung or in the circulating blood

It is well known that strong kininase activity exists in the lung and more than 80 per cent of the blood kinin is destroyed while passing through the pulmonary circulation [16] *Also half life of* synthetic bradykinin in blood was shown to be within 0 5 minute [17] Our recent study[18] indicated that kininase activity decreased after acute myocardial infarction in survivors *but remained normal* in patients who died of shock A normal kininase activity might lead to rapid and significant inactivation of kinin Thus, the observed changes in *kinin system substances* in non survivors could be attributed to kininase activity in circulating blood

There are discrepancies between our observations of kinin in shock states and those of other investigations Sicuteri and colleagues[3] reported that blood kininogen levels decreased in the initial several days after acute myocardial infarction and that such a decrease in kininogen was more pronounced in non survivors corresponding to a significant lowering of blood pressure They concluded that kinin system substances are responsible for the genesis of cardiogenic shock Dzizinskii and co workers[6] compared kininogen levels in patients with an inactive form of coronary insufficiency, angina pectoris acute myocardial infarction and cardiogenic shock, and found that kininogen levels depended on the severity of the diseases Wiegershausen and associates also deduced that kinin is one of the causes of cardiogenic shock from their observation of decreases in kininogen in patients with acute myocardial infarction

Thus most of the authors concluded that the activated kinin induced hypotension which might be a cause of shock This was based upon the observations that kininogen decreased in the *initial stage of myocardial* infarction and that changes were more prominent in cardiogenic shock Our observations on the other hand are in accord with that of Wilson and colleagues[19] who *failed to find significant* differences in kininogen between shock and non shock patients

It is necessary to emphasize that most of the above conclusions are based on *measured decreases in kininogen* levels with only indirect estimates of increases in kinin levels As already mentioned our recent study[18] indicates that kininase activity was low in patients without shock *in myocardial infarction* whereas strong normal kininase activity was found in patients who died of shock These observations would indicate that the released kinin might remain longer in the blood of survivors than in the blood of non survivors This suggests that the kinin released in patients with infarction might actually be beneficial rather than a cause of cardiogenic shock

Recently vasodilator therapy by reducing the afterload of the heart, [20,21] has been reported to be

a valuable mode of treatment during cardiogenic shock or congestive heat failure following acute myocardial infarction As kinin appears to have a potent coronary and peripheral vasodilating action the beneficial effects of endogenously released kinin can be considered in patients with acute myocardial infarction

Kinin has also recently been proposed to be a mediator of prostaglandins which regulate coronary blood flow [2, 23] Further studies might clarify these mechanisms in acute myocardial infarction

Summary

Kinin is known to have potent pain producing and hypotensive actions and has been suggested as one of the causes of chest pain and shock in acute myocardial infarction Since most of the previous reports[3] have been based on measurements of kininogen the inactive precursor of kinin peripheral blood kinin as well as kininogen was measured in this study Kinin and kininogen levels were determined over a period of one month or until death from the onset in 23 cases of acute myocardial infarction along with simultaneous measurements of hemodynamic indices Sixteen of the 23 cases survived more than one month and seven patients died of pump failure within 3 days of the infarction In the survival group increased kinin and decreased kininogen levels were observed in the initial stage reaching a maximal change on the second day The alterations in kinin levels were significantly correlated with concomitant lowering of blood pressure decreased total vascular resistance and prolongation of circulation time In the non survival group there was no increase in kinin levels in spite of a decrease in kininogen Accordingly no significant correlation was found between kinin and hemodynamic changes The lack of change in kinin in the latter group was thought to account for the strong kininase activity Thus these data indicate that kinin is *not the* cause of cardiogenic shock Rather the increased kinin level observed in survivors might indicate beneficial vasodilation effects possibly by increasing coronary flow and reducing the afterload of the left ventricle

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Chlamydia trachomatis endocarditis

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The clinical diagnosis of infective endocarditis may be difficult to ascertain especially if multiple blood cultures are negative and complicated clinical circumstances further mask the actual pathologic process

The true incidence of negative blood cultures in the presence of active infective endocarditis is not known since many factors are involved The reported incidence varies from 0 to 40 per cent Papers from Great Britain and Australia mention negative blood cultures accompanying endocarditis due to *Coxiella burnetti* Blood cultures were also negative in a Scottish report of two cases of active infective endocarditis due to *Chlamydia psittaci* occurring on previously damaged valves

The major purposes of this paper are (1) to report a case of *Chlamydia trachomatis* endocarditis and to underscore the specialized modalities which may be needed to establish the diagnosis (2) to bring to the attention a new echocardiographic finding

The patient was a 25 year old woman of 30 weeks gestation who presented with fever and multiple negative blood cultures and died after a short fulminating clinical course Studies performed after death allowed clarification of a puzzling clinical picture

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Case report

A 25 year-old pregnant woman of 30 weeks gestation was admitted to the Cincinnati General Hospital on August 21 1976 with a five day history of discomfort in the left side of the neck and left shoulder One day prior to admission she experienced nausea vomiting malaise and feverishness She had noted a malodorous vaginal discharge on several occasions but her pregnancy had been otherwise uncomplicated She denied cough abdominal discomfort headache dyspnea or skin rash. The past medical history was unremarkable and she was on no medications

Admission physical examination revealed blood pressure of 132/64 mm Hg pulse 120/minute respirations 20/minute and temperature 103 F (39 4 C) The skin and mucous membranes were unremarkable No nuchal rigidity was present The lung fields were clear A Grade 1/6 systolic ej ction murmur was audible in the second and third left intercostal spaces and a ventricular gallop rhythm was present The uterus was approximately thirty weeks gestational size with fetal heart tones of 190 per minute A small amount of white cervical discharge was present. Neurological examination was unremarkable

Initial laboratory data included white blood count ,000/mm. with 58 per cent segmented neutrophils 28 per cent band forms 11 per cent lymphocytes and 3 per cent monocytes hemoglobin 10 9 Gm per cent hematocrit 34 per cent and erythrocyte sedimentation rate 88 mm /hour (Westergren) The BUN electrolytes and SMA 12/60 were normal Urinalysis showed 6 to 8 white blood cells per high power field and no organisms on gram stain X rays of the chest and left shoulder as well as the electrocardiogram were unremarkable Data subsequently obtained included antistreptolysin 0 titer less than 166 Todd units negative latex fixation test for rheumatoid factor negative intermediate strength purified protein derivative tuberculin test Histoplasma complement fixation titer 1 8 and negative antinuclear antibody test Four sets of aerobic and anaerobic blood cultures were negative Urine culture was negative and culture of the cervical discharge grew only a few *Staphylococcus epidermidis* An echocardiogram demonstrated a posterior pericardial effusion with no abnormalities of the aortic valve and no diastolic fluttering of the mitral valve (Fig 1)

On the second hospital day a to and fro aortic murmur was suspected but subsequently a loud tri phasic pericardial friction rub became audible and no separate murmur could be detected A therapeutic trial of salicylates produced initial

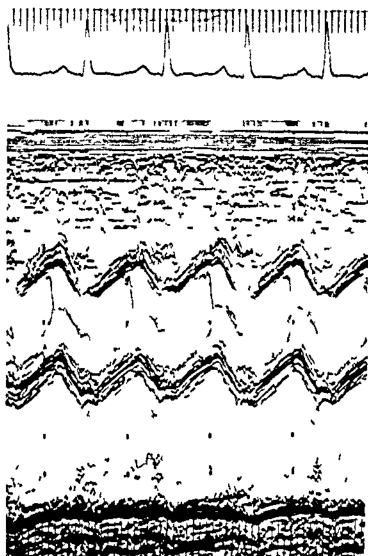


Fig 1 Echocardiogram at the aorta and left atrium performed early in the patient s hospital course The aortic valve leaflets are thin and the aortic walls are not abnormally thickened

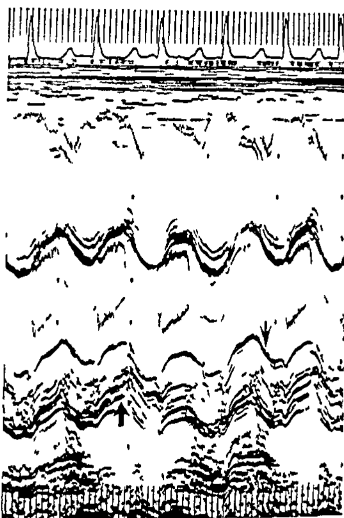


Fig 2 Repeat echocardiogram at the left atrium and aorta performed one day before death The posterior aortic wall *(thin arrow)* is well visualized An abnormal dense echo *(thick arrow)* with motion parallel to the aortic wall is present The aortic leaflets show systolic fluttering but are not abnormally thickened

subjective improvement but chest pain subsequently returned On September 1 Prednisone in a dose of 60 mg per day was begun with a presumptive diagnosis of idiopathic pericarditis

Three days later the patient was found unconscious but awoke several minutes later demonstrating a transient right sided hemiparesis She had a blood pressure of 130/50 mm Hg with no paradoxical arterial pulse normal venous pressure and clear lung fields The friction rub persisted Arterial blood gases showed a pH of 7 34 pCO 22 and pO 96 while the patient was receiving nasal oxygen at 3 liters per minute The electrocardiogram showed sinus tachycardia and S T segment depression in the inferior leads Chest radiogram showed enlargement of the cardiopericardial silhouette Lumbar puncture revealed 40 red blood cells per mm of cerebrospinal fluid A second echocardiogram demonstrated both anterior and posterior pericardial effusions normal mitral and aortic valve echoes and an abnormal dense echo in the region of the aortic root and left atrium which moved parallel with the posterior aortic wall (Fig 2) This echo could not be eliminated by changes in gain or minor changes in transducer angulation Consideration of pericardiocentesis or aortic angiography was postponed pending possible evacuation of the uterus

The patient became increasingly dyspneic and developed signs of pulmonary edema A Swan Ganz catheterization revealed the following pressures right ventricle 65/3 pulmonary artery 63/17 and pulmonary wedge pressure of 26 Cardiac arrest occurred and the patient was successfully resuscitated Fetal heart tones were no longer audible Following several more arrests she could no longer be resuscitated and she died on September 7 1976

Necropsy The necropsy was performed 26 hours after death The major pathologic findings were confined to the heart except for a hemorrhagic cortical infarction in the right cerebral hemisphere and recent acute bronchopneumonia of a few days duration The pericardial sac contained 550 ml of clotted blood The visceral epicardial surface was diffusely covered by a thick shaggy fibrinous exudate which was most marked surrounding the root of the great vessels The heart weighed 520 Gm and showed left ventricular hypertrophy There was no evidence of any congenital cardiac anomaly or healed rheumatic valvular disease A vegetation with finger like projections (Fig 3) sat on the ventricular surface of the



Fig 3 View of left ventricular outflow tract and the opened ascending aorta with the origin of major branches at the arch At the root of the aorta the intact right and non coronary cusps are clearly visible The left coronary cusp shows just below its rim the v g tation with the fin er like projections and an oval shaped ring abscess The gaping opening in the endocardial surface is located immediately below the left coronary cusp with its vegetation and to the left of the ring abscess. Ao = aorta ascending RAb = ring abscess

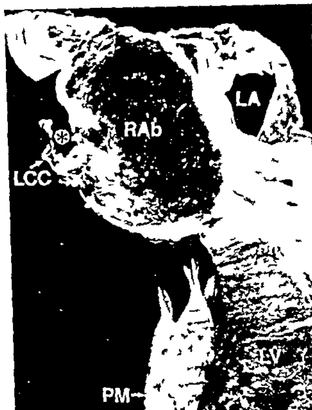


Fig 4 Section through arotic valve with ring abscess left atrium and left ventricular wall with infarcted papillary muscle The abscess reaches cephalad and above the upper margin of the cusps of the aortic valve * = sinus of Valsalva LA = left atrium LCC = left coronary cusp LV = left ventricle PM = papillary muscle RAb = ring abscess

left coronary cu p of the aortic valve Just caudal to it the cusp showed a small probe patent perforation Immediately below the base of this u p a large slit like gaping and clot filled opening led into a cavity of 1 5 × 0 5 cm (Fig 3) This cavity was contiguous with an aortic ring abscess of 2 × 2 × 1 cm (Fig 4) in a cephalad direction while caudally it extended between the endocardial surfaces of the anterior mitral leaflet Here it ontinued into three bulging lesions which protruded from the atrial surface of the base of the mitral cusp (Figs 5 and 6) They measured up to 1 × 1 5 cm in largest diameter The destructive process also involved part of the commissure between the left and non-coronary cu ps so that a communi cation existed between the sinuses of Valsalva of each of these cusps The ontour and delicate structure of the non-coronary and right coro ry usps were preserved Blood clot filled a rupture ite of the sinus of Valsal a behind the left coronary cusp (Fig 6) This explained the leakage of blood into the pericardial sa which appeared to have been late in the patient s course The aortic valve endocarditis was further complicated by cute infarction of the anterior and posterior papillary muscles of the left entricle Routine culture of the vegetation and ring abscess yielded growth only of contami nants. Histologic examination revealed an acute inflamma tory necrotizing process at the aortic ring Cloudy amorphous material in the aortic valve vegetation was surrounded by macrophages polymorphonuclear leucocytes and marked edema

Grocott and Ziehl Nielsen stains were n gative The Gram stain and numerous others including the Macchiavello and Giménez stains were equivocal Giemsa and indirect fluores cent stains of formalin fixed sections were nonrevealing The fibrinous pericarditis was organizing and consistent with a few weeks age Ultrastructural studies were performed on one of the finger like projections of the vegetation

For electron microscopy formalin fixed tissue was washed in cacodylate buffer refixed in 4 per cent cacodylate buffered gluteraldehyde post osmi ated dehydrated and embedded in epoxy resin Thin sections were photographed in a Siemens Elmiscop 101 electron microscope

Considerable autolysis was exhibited by the cells making up the vegetation with the host cells being more degenerated than either the inter or intracellular organisms Remnants of cytoplasmic vacuoles were found in which were located various stages in the developmental cycle of the contained organisms (Fig 7) Three different forms of the organism could



Fig 5 Inflow tract of left ventricle Three bulging lesions protrude from the atrial surface of the basal portion of the anterior mitral leaflet *AL* = anterior leaflet of mitral valve *APM* = anterior papillary muscle *LA* = left atrium



Fig 6 Sagittal section through left ventricle and left atrium demonstrating left ventricular in and outflow tracts The destructive and extensive nature of the process is evident and also the contiguity and relationship between the lesions in the aortic valve the aortic wall and the anterior leaflet of the mitral valve The rupture site of the sinus of Valsalva is also clearly visible *Ao* = ascending aorta *H* = hemorrhage due to rupture of sinus of Valsalva *LA* = left atrium *LV* = left ventricle *PPM* = posterior papillary muscle *R* = rupture site sinus of Valsalva of left coronary cusp

be distinguished The Initial Body was characterized by a uniform dispersal of ribosomes and little or no condensation of chromatin these represented the pre division stage of devel opment after entry into the cell (Fig 8) The Initial Body as well as all other stages was surrounded by a plasma membrane plus a rudimentary cell wall (Fig 8) The Interme diate Body contained dispersed ribosomes and an increasingly obvious condensation of chromatin (Fig 9) The Elementary Body was marked by dense condensation of all cell contents and a reduction in over all dimension (Fig 10)

Serology Two retrieved serum samples which had been collected on August 23 and August 28 15 and 10 days premortem respectively were tested by the microimmuno fluorescence method for antibodies to *Chlamydia trachoma tis* A thirty two fold rise in the IgM antibody and a sixteenfold rise in the IgG antibody to immunotype F antigen were demonstrated (Table I) There was cross reaction with type G antigen The serum sample collected on August 28 (10 days premortem) also contained cross reacting IgM antibody to types E D and L_2 and IgG antibody to types H I K E D and L_2 There was a stable IgG antibody titer of 1 64 but no IgM antibody to type J antigen The IgG antibody to type J antigen also cross reacted with type C antigen

Both serum samples were tested for antibody to *Coxiella burnetti* by the microagglutination and microimmunofluores cence methods The results were negative Complement fixation tests for antibody to *Chlamydia psittaci* and *Chla mydia trachomatis* were performed on both serum samples but the serum was anticomplementary

Comments

The *Chlamydiae* are a group of organisms that have a rudimentary bacteria like cell wall and multiply by binary fission They contain both DNA and RNA but are unable to sustain growth outside an animal cell They are also susceptible to a number of antimicrobial agents Thus their obligate intracellular growth is more like those of viruses but their biochemistry and molecular structure are more like bacteria [6] There are pres ently two species in the family *Chlamydiaceae*

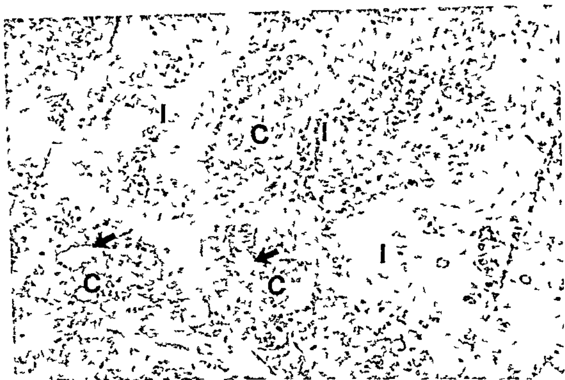


Fig 7 Survey view of host cells *(C)* demonstrating partial autolysis and Chlamydia *(illustrated at arrows)* in different developmental stages Interstitial fibrin is indicated by *I* (Original magnification ×6 750)



Fig 8 Initial Bodies *(IB)* are characterized by relatively large size as compared to the Intermediate Body *(IF)* and by the paucity of chromatin Each organism is surrounded by a plasma membrane *(thin arrow)* and by an external rudimentary cell wall *(thick arrow)* (Original magnification ×43 800)



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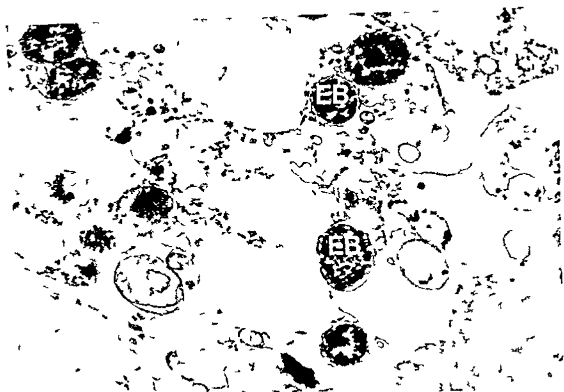


Fig 10 The Elementary Body *(EB)* is seen intermixed with cell debris Some filaments of fibrin are *in the lower right corner* This is the infective form which is taken up by a cell to begin the reproductive cycle Note the thin wavy cell wall surrounding each organism (Original magnification ×25 6 0)

Table 1 Serum antibody to *Chlamydia trachomatis* by the microimmunofluorescent antibody test*

Nature of antibody	*Date of serum*	*Immunotype antigen of Chlamydia trachomatis*													
		C	*J*	*A*	*H*	*I*	*K*	*B*	*E*	*D*	*L*	*L*	*L*	*G*	*F*
IgM	8/?3/ 6	–	–	–	–	–	–	–	8†	–	–	–	–	8	16
	8/28/76	–	–	–	–	–	–	–	128	64	–	1?8	–	128	512
IgG	8/23/ 6	3?	64	–	–	–	–	–	–	–	–	–	–	8	16
	8/?8/76	16	64	–	3?	16	8	–	128	16	–	?56	–	1?8	256
IgM IgA	8/?3/ 6	16	64	–	–	8	8	–	8	–	–	–	–	8	16
–IgG	8/28/ 6	16	64	–	3?	3?	–	–	1?8	64	–	?56	–	64	256

Kindly performed by Sa pin Wang M D Dep rtment of P th biol gy School of Publ H lth a d Commun ty Med cin Un v rsity of Washingt n Se ttle Wa h.
– = <8
† = reciprocal f th serum d lution

suspected as the causative organism and tissue cultures were not performed Complement fixa tion test for antibody to *Chlamydia psittaci* was of no value because the patient s serum proved to be anticomplementary The equivocal results of special stains which are usually utilized to demonstrate chlamydia were probably due to autolysis and demanded more sophisticated methods of examination The subsequent finding of Chlamydia in the vegetation by electron microscopy warranted further in depth serologic studies

The thirty two fold rise (from 1 16 to 1 512) in the patient s IgM antibody to immunotype F *Chlamydia trachomatis* during her brief illness indicates that she was in the acute stage of *Chlamydia trachomatis* infection most likely due to immunotype F organism It is known that antibody to type F antigen commonly cross reacts with type G antigen [9] The serum sample

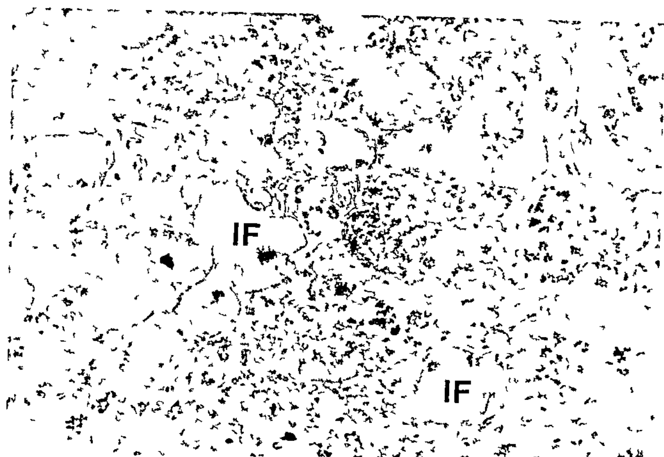


Fig 9 Intermediate Bodies *(IF)* have disperse ribosomes and the beginning condensation of chromatin (Original magnification ×17 300)

namely *Chlamydia psittaci* which primarily produced diseases in mammals or birds and can be transmitted to man resulting in psittacosis and ornithosis and *Chlamydia trachomatis* which causes primary diseases in humans such as trachoma inclusion conjunctivitis lymphogranuloma venereum urethritis and cervicitis [9] One recent report also implicated *Chlamydia trachomatis* in a distinctive pneumonia syndrome in black infants 4 to 24 weeks of age [10]

All Chlamydiae are characterized by complex cycles of multiplication [11, 12] Electron microscopic studies of appropriately infected tissue culture cells show that the first stage of infection consists of uptake of an Elementary Body (Fig 10) by the host cell into a cytoplasmic vacuole [13] A group of vacuoles then coalesce and form an inclusion body containing many organisms which have transformed their structure into that of the Initial Body (Fig 8) The Initial Body undergoes one or more divisions and then following the last division the organisms begin to condense into Intermediate Bodies (Fig 9), and finally are released into the intercellular space as Elementary Bodies which can then begin a new cycle of infection In our present case it was not possible to locate a membrane surrounding all of the inclusion bodies One of the distinguishing characteristics of *Chlamydia psittaci* is the disappearance of the inclusion body membrane during the late stage of division [14] Since the host cells in the present case were extensively autolyzed the lack of such a membrane has little diagnostic significance Occasional giant forms which appeared to reproduce by budding rather than by division were reported in *Chlamydia trachomatis* growing in tissue culture [15]

The diagnosis of *Chlamydia trachomatis* endocarditis in our patient was retrospective Further diagnostic procedures were performed after the usual causes of infective endocarditis were excluded The unusual finger like vegetations reminded one of us (C W) of similar findings in two previously reported cases of *Chlamydia psittaci* endocarditis [4] However these occurred on previously damaged valves and in patients who both had pulmonary psittacosis as well Our patient had no exposure to birds and there was no evidence of pulmonary psittacosis In addition her active infective endocarditis occurred on a previously normal aortic valve At the time the autopsy was performed Chlamydiae were not

Since *Chlamydia trachomatis* genital infections are widespread it is conceivable that many cases of *Chlamydia trachomatis* endocarditis remain undiagnosed The micro immunofluorescence test for antibody to *Chlamydia trachomatis* is a valuable diagnostic tool [6] In a patient with a clinical picture compatible with infective endocarditis and negative blood cultures a fourfold or more rise in IgM antibody to *Chlamydia trachomatis* is highly suggestive of *Chlamydia trachomatis* infection If surgery is carried out the diagnosis can further be confirmed by tissue culture for chlamydia immunofluorescence staining and ultrastructural examination of the affected tissue

The ability of the echocardiogram to delineate valvular vegetations is well recognized We have been unable to find previous reports of echocardiographic abnormalities associated with an aortic valve ring abscess The unusual echo from the region of the aortic root and left atrium which developed during the course of this patient s illness is similar to that reported in several other circumstances The presence of an abnormal echo with motion parallel to the posterior aortic wall along with simultaneous visualization of normal valve leaflets is consistent with aortic dissection [12] The specificity of this pattern however has been questioned by Brown and colleagues [14] who reported similar findings in normal subjects and suggested that echos were being reflected from both sides of the aortic-left atrial wall Other sources of an abnormal echo from the region of the aortic root and left atrium include effusion in the transverse sinus of the pericardium and echos from the left atrial insertion of the pulmonary veins However motion of the abnormal echo parallel to the aortic wall is not to be expected in these cases The failure to eliminate the abnormality with changes in gain or transducer angulation militates against mere technical problems

Examination of the pathological specimen in this case (Fig 4 and diagram Fig 11) illustrates that the echobeam in a plane which would pass through the aortic valve leaflets would next pass through the valve ring abscess before entering the left atrium We feel therefore that in this case the abnormal echocardiographic finding represents echocardiograhic detection of the abscess The possibility that the abnormal echo was reflected from the dilated sinus of Valsalva must be considered but the relative locations of the sinus and the abscess in the projected path of the echobeam favors our former interpretation

The echocardiogram of this patient did fail to demonstrate vegetations on the aortic valve leaflets This was probably due to the location of the vegetations on and restricted to the left coronary leaflet since this leaflet is not routinely visualized by current techniques In retrospect the scan from the tip of the mitral valve to the aorta did reveal some dense echos from the region of the base of the mitral valve (Fig 12) This probably represents the vegetations found at the base of the anterior mitral leaflet (Figs 5 and 6)

The degree of destructiveness of the pathologic process in our patient was indeed marked Arnett and Roberts in their necropsy study of patients with active infective endocarditis found that the type or virulence of an organism did not play a significant role in the development of a ring abscess In view of the clinical presentation of our patient and the findings at necropsy their report is of further interest Aortic ring abscess occurred commonly and was also the most common cause of pericarditis in patients with active infective encocarditis Only half of all their cases with pericarditis had clinical evidence of it The aortic valve was the one almost exclusively affected by a ring abscess and if so always was accompanied by aortic valve regurgitation Retrospectively our patient had four of the five features which according to them serve as clinical clues to the presence of a valve ring abscess (1) pericarditis (2) aortic valve involvement (3) evidence of valvular regurgitation of recent origin and (4) recent origin and short duration of symptoms leading to severe debility or death A V block was not present It appears therefore that when a patient presents with a clinical picture of fulminant infection and has evidence of pericarditis the diagnosis of endocarditis with an aortic ring abscess should not be easily dismissed

We conclude that (1) *Chlamydia trachomatis* must now be added to the list of organisms that may cause infective endocarditis with negative blood cultures (2) *Chlamydia trachomatis* must be considered in addition to *Neisseria gonorrhea* [2] to be another venereal disease causing microorganism that is potentially capable of producing infective endocarditis of a normal heart valve (3) the echocardiographic abnor

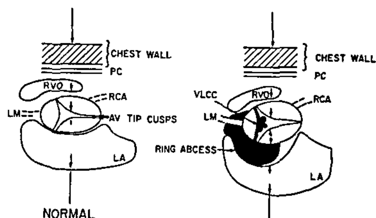


Fig 11 *Vertical arrows indicate course of echobeam* On the left side is a diagram of the course of the echobeam through cardiac structures in the normal heart On the right the diagram depicts the course of the echobeam through cardiac structures of our case It explains why the aortic vegetation on the left coronary cusp was not visible on the echocardiogram because it was not located in the course of the echobeam The *(black)* ring abscess on the other hand is located in the course of the beam and it explains the changes in the aortic wall visible in the echogram Compare with *Figs 4* and *6* *AV* = aortic valve *LA* = left atrium *LM* = left main coronary artery *PC* = pericardium *RCA* = right coronary artery *RVO* = right ventricular outflow tract *VLCC* = vegetation on left coronary cusp

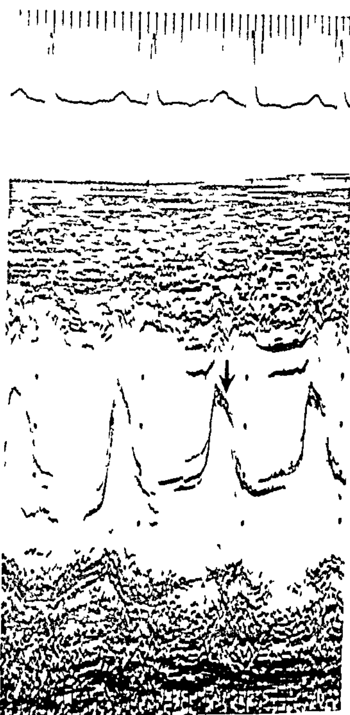


Fig 12 Portion of an echocardiographic sweep from the mitral valve to the aorta As the transducer approaches the aorta increased echoes are seen from the anterior mitral leaflet *(arrow)*

collected on August 28 also contained IgM antibody extensively cross reacting with antigens of E O and L immunotypes This cross reaction was rather unusual It has been shown that IgM antibody may disappear within one month after acute chlamydial infection [7] The stable IgG antibody titer of 1 64 to type J antigen but no IgM antibody probably indicates that the patient had previous *Chlamydia trachomatis* type J infections It is also known that antibody to type J antigen cross reacts with type C antigen [8] Our patient had a history of vaginal discharge early during her pregnancy Although no definitive diagnosis was made it is very tempting to speculate that it might have been due to *Chlamydia trachomatis* type J genital infection

Chlamydia trachomatis causes both ocular and genital diseases in humans [8] There was no evidence of eye disease in our patient However, she did have vaginal discharge Although the cervical discharge was not cultured for chlamydia, it is most likely that she had genital *Chlamydia trachomatis* infection It is not clear why she had hematogenous dissemination leading to infection of the aortic valve She had no apparent underlying cardiac disease and there was no evidence of previous valvular disease While the results of the serologic studies indicate evidence of an active infection with *Chlamydia trachomatis* type F (irrespective of site or source) and the ultrastructural findings in the valve vegetation reveal Chlamydia (irrespective of subtype) only the combination of the two substantiates in our case the diagnosis of *Chlamydia trachomatis* endocarditis

Electrocardiographic changes simulating acute myocardial infarction caused by hyperkalemia Report of a patient with normal coronary arteriograms

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Electrophysiological effects of moderate to severe hyperkalemia and its effect on the electrocardiogram have been well described by various authors Shortening of QT interval tenting of T waves lengthening of PR interval loss of P wave causing sinoventricular rhythm and finally broadening of QRS and sine wave are some of the more commonly described abnormalities ST segment changes resembling a current of injury have been rarely reported [5] However in none of the previously reported cases was coronary artery disease ruled out with any certainty

We observed a patient with diabetic ketoacidosis and hyperkalemia who showed marked ST segment elevations resembling acute anterior wall myocardial infarction Treatment of hyperkalemia resulted in prompt return of the ECG towards normal Subsequent work up including exercise testing and selective coronary arteriography ruled out any significant coronary artery disease suggesting that the ECG changes were probably caused by hyperkalemia

From th Di is of Ad lt Cardiol gy Cook Cou ty H p tal Ch g Ill.

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Atte ding Physicia Di ision f Adult Cardiol gy and Director Non as e Laboratory Cook Cou ty Hosp tal, Ch g Il
Chairman, Division of Ad lt Cardiology Cook C nty Hospital, Ch go Ill.

Case report

G C a 48-year old black male was admitted to Cook County Hospital because of diabetic ketoacidosis The patient was a known diabetic for the last 1? years controlled with 4? units of NPH insulin Two weeks prior to admission he had d veloped mild fever and a non productive cough He had also noted fatigue weakness, and dyspnea on moderate exertion He also complained of nausea and had vomited a few times The patient denied any history of chest pain In the past he had been treated for pulmonary tuberculosis There was no history of hypertension The patient had smoked 20 to 40 ci arettes a day for about 30 years

On examination the patient was a moderately built although somewhat undernourished black male in mild respiratory distress He was drowsy but well oriented The heart rate was 1?0 beats/minute blood pressure 150/80 mm Hg temperature 99 F and respiratory rate 28/minute The skin was dry and neck veins were flat CVP measured 1 0 cm of H O The lungs showed slightly decreased breath sounds in right upper zone Examination of the heart was entirely normal Specifically no S_3, S or friction rub was heard by any examiner

Initial laboratory data showed marked hyperkalemia acidosis hyperglycemia and ketonemia compatible with the picture of severe diabetic ketoacidosis (see Table I) The ECG on admission showed marked ST segment elevation in Leads V V and avL suggestive of acute anterior wall injury There were also tall peaked T waves in the Leads V through V compatible with hyperkalemia (see Fig 1 *upper panel*) With the presumptive diagnosis of acute myocardial infarction the patient was transferred to the ICCU where close monitoring and tandard treatment of acute diabetic ketoacidosis consisting of regular insulin sodium bicarbonate and fluid replacement was instituted Serial ECGs and enzymes determinations were obtained Over the next ?4 to 48 hours the patient showed marked improvement in his general condition as well as in the biochemical data His blood sugar came down

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mality herein described must be added to the list of manifestations of bacterial endocarditis and also to the differential diagnosis of apparent abnormal widening of the posterior aortic wall

Summary

A case of infective endocarditis due to *Chlamydia trachomatis* immunotype F is reported Multiple negative blood cultures were a major deterrant from the initial clinical diagnosis of infective endocarditis Postmortem ultrastructural identification of Chlamydia in the aortic valve vegetation led to an intensive retrospective study of retrieved serum samples utilizing microimmunofluorescent tests Likewise an unusual echocardiographic finding was discovered to be the ultrasonic visualization of an aortic ring abscess No similar case could be found in the literature

Clinicopathologic correlations are presented

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Fig 2 Coronary arteriograms A Left coronary artery in the left anterior oblique (60 degree) projection and B right coronary artery in the left anterior oblique (40 degree) projection showing all branches widely patent

Table I Laboratory data

	Date	Time	Serum K (mEq/L)	pH	Serum glucose (mgm %)	S bicarb (mEq/L)	ECG
A	11/8/76	1 20 A M	8 3	7 09	840	6 8	Injury pattern and tented T waves
B	11/8/76	7 10 A M	4 3	7 35	348	14 1	Slight ST elevation and tented T waves
C	11/10/76	7 00 A M	4 0	7 44	45?	25 6	Normal

The hyperkalemia of ketoacidosis differs from that of other causes in that there is a shift of potassium out of the cell resulting in an altered ratio of intracellular to extracelluar potassium [3,4] This may contribute in part to the severity of the ST segment elevations in the setting of diabetic ketoacisosis It is also possible that the associated severe acidosis and marked hyperglycemia present in our patient may have added to the effect of hyperkalemia in producing the observed ECG changes

Electrocardiographic abnormalities resembling myocardial infarction in the presence of severe hyperkalemia have been reported by several observers in the past [1-5] Pathological Q waves as well as ST T changes resembling acute injury pattern have been described separately The appearance of pathological Q waves has generally been attributed to altered initial QRS forces secondary to intraventricular conduction abnormalities resulting from hyperkalemia [3]

Levine and associates[3] reported four cases of acute renal failure with hyperkalemia and ST T patterns suggesting myocardial infarction In all of these patients lowering of the serum potassium level by hemodialysis was associated with return of the electrocardiogram towards normal However in two of the four patients fibrinous pericarditis was noted to be present at autopsy and this may have had an effect on the ECG of these two patients In the third patient a left bundle branch block pattern was present which of course renders the ECG diagnosis of acute myocardial infarction difficult The fourth patient was not autopsied so that neither coronary artery disease nor pericarditis both of which can be associated with renal failure were ruled out

Gelzayd and Holzman[2] reported a case of diabetic ketoacidosis with hyperkalemia presenting with ECG abnormalities similar to that of our patient However neither coronary arteriography nor exercise testing was reported as performed in their patient

Lichstein and colleagues[4] reported two patients with hyperkalemia induced fascicular block one of whom had marked ST segment elevation in Leads V and V_2 similar to those of our patient The resemblance of the ST T changes to those of

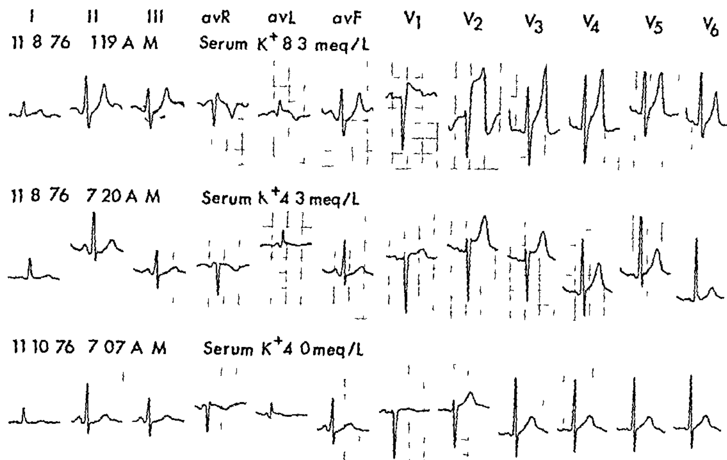


Fig 1 Serial electrocardiograms *The top panel* represents a twelve lead ECG on admission showing marked ST segment elevations in Leads V V and avL *Middle panel* shows same twelve leads six hours later when the serum potassium has come down to 4 3 mEq /L Notice the marked improvement in the ST segment elevation and T wave abnormality Lower panel recorded two days later shows normal ECG when serum K is 4 0 mEq /L

from 840 to 452 mg per cent The serum K came down from 8 3 to 4 0 mEq /L and the pH increased from 7 09 to 7 44 (see Table 1) The electrocardiogram taken six hours after admission when the serum K had came down to 4 3 mEq /L showed marked decrease in the ST segment elevation However slight J point and early ST segment elevation and some T wave tenting persisted (Fig 1 *middle panel*) Subsequent ECGs two and three days later were completely within normal limits (Fig 1 *lower panel*) Slight QRS prolongation which had been noted on the admission ECG was absent in subsequent tracings The frontal plane QRS axis remained unchanged throughout the patient s course The cardiac enzymes remained grossly within normal limits The patient made an uneventful recovery and was placed back on NPH insulin

Ten days later a treadmill exercise test was performed using the Bruce protocol The patient reached the predicted level of 6 to 7 mets and a maximal heart rate of 150 beats/minute (87 per cent of maximum predicted for the age) The ECG did not show abnormal ST segment changes or arrhythmia and the patient did not complain of chest pain The test was considered negative for ischemic response

Cardiac catheterization was performed two weeks after the admission and selective coronary arteriograms were obtained in multiple views Both the left and right coronary arteries and their major branches were visualized and appeared completely free of any obstructive lesions (Fig 2) Left ventricular function was also normal with an ejection fraction of 69 per cent

Discussion

Increased plasma potassium may occur spontaneously or iatrogenically Some of the more frequent clinical causes include renal failure untreated diabetic ketoacidosis adrenocortical insufficiency, and over enthusiastic therapeutic use of potassium salts or drugs with high potassium content

An increase in the concentration of extracellular potassium lowers the resting membrane potential leading to a reduction of the upstroke velocity amplitude and duration of the action potential This effect has been recorded in atrial ventricular and Purkinje fibers and may be manifested on the ECG by changes in the amplitude and duration of the P wave and QRS complex[4 8] The mechanism of T wave and ST segment changes is not well understood and has not been well correlated with action potential abnormalities

Low renin (primary ') hyperaldosteronism

Differential Diagnosis and Distinction of Sub-Groups Within The Syndrome

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In an earlier paper we discussed the clinical biochemical and pathological features of low renin hyperaldosteronism (primary hyperaldosteronism) This review is concerned with the differential diagnosis of the condition and a third paper describes treatment

Primary hyperaldosteronism is usually associated either with a unilateral adrenocortical adenoma or with bilateral hyperplasia of the zona glomerulosa rarely the syndrome may be associated with an adrenal or other carcinoma and very occasionally the abnormalities are reversible by glucocorticoids To facilitate treatment these several forms must be differentiated one from another

As a group however such patients must first be distinguished from those suffering from other varieties of hypertension with mineralocorticoid excess and from those cases of apparently essential hypertension with renin suppression A classification of hypertension associated with mineralocorticoid excess is shown in Table I Part I of this paper describes the differential diagnosis of primary hyperaldosteronism part II describes the distinction of the various forms within the syndrome

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Part I The differential diagnosis of primary hyperaldosteronism

Conditions with which primary hyperaldosteronism may be confused are outlined in Table I

Secondary hyperaldosteronism Primary and secondary hyperaldosteronism can be differentiated by measurements of renin and angiotensin II in plasma In the latter aldosterone excess results from increased circulating levels of renin and its active product angiotensin II which in turn result usually from sodium depletion or renal disease[3] By contrast primary hyperaldosteronism is associated with inappropriately low circulating levels of renin and angiotensin II[1] Even without such measurements plasma sodium serves as a rough guide to renin levels as plasma renin concentration and plasma sodium are inversely correlated in hypertension[4] Thus in a patient with hypertension and hypokalemia in whom aldosterone excess is shown or suspected, hyponatremia points to a cause associated with high renin levels while a high plasma sodium suggests primary hyperaldosteronism

The common causes of secondary hyperaldosteronism with hypertension are outlined below (see Table I)

Hyperaldosteronism due to diuretic therapy This is probably the most frequent cause of aldosterone excess in hypertensive patients Diuretic induced sodium loss leads to a secondary elevation of renin angiotensin II and aldosterone[3] Its importance is that it may mimic or obscure other causes of hyperaldosteronism If

acute anteroseptal myocardial infarction is evident from their Fig 1 although the authors do not call attention to this point The pattern is described as showing right bundle branch block and left anterior hemiblock However, these conduction abnormalities unlike left bundle branch block do not by themselves explain the observed ST T changes

The findings in our patient reemphasize the previously reported observation that hyperkalemia may produce marked ST T changes resembling those of acute myocardial infarction To the best of our knowledge there is no previous report in the literature of a patient with the hyperkalemia induced ECG changes of acute myocardial infarction in whom coronary artery disease was judged unlikely on the basis of negative exercise electrocardiography or ruled out by normal selective coronary arteriograms We would conclude that hyperkalemia should be considered in the differential diagnosis of ST T changes resembling acute myocardial infarction especially when these occur in those clinical settings where hyperkalemia is frequently observed

Summary

A patient is described with severe diabetic ketoacidosis and hyperkalemia who presented with an ECG resembling an acute anterior wall myocardial infarction Treatment of hyperkalemia resulted in prompt return of the ECG towards normal Subsequent work up including exercise testing and selective coronary arteriography ruled out any significant coronary artery disease suggesting that the ECG changes were probably caused by hyperkalemia While similar changes have rarely been described in the past this would appear to be the first such case in whom coronary artery disease was ruled out by a negative exercise testing and coronary arteriography

We thank Miss Suzanne Adams for her expert secretarial assistance

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terone point to a renal rather than an adrenal abnormality The diagnosis is confirmed by demonstrating higher concentrations of renin and angiotensin in the renal vein of the affected side compared with the opposite in the absence of renal artery stenosis and by the radiological appearances on selective renal arteriography The lesion is usually a benign juxta glomerular cell tumor rich in renin removal of the affected kidney will reverse both the hypertension and the biochemical abnormalities

Congenital hyperaldosteronism Prior to the era of renin assays a number of children and young adults were described with hypertension and hyperaldosteronism in whom total or sub total adrenalectomy often resulted in a marked blood pressure fall Adrenocortical adenomas were not found and the glands showed either adrenocortical hyperplasia or normal histology Several had symptoms dating back to infancy or early childhood and some were mentally or physically retarded the term congenital aldosteronism has been applied to this group In the absence of renin measurements it is difficult to exclude the possibility that hyperaldosteronism was secondary to unrecognized renal disease to malignant hypertension (which was present in some [3] or even to a renin secreting renal tumor However such causes seem less likely in those who showed a sustained blood pressure fall after adrenalectomy

Hypertensive disease of pregnancy Normal pregnancy is associated with marked increases in plasma concentrations of renin renin substrate angiotensin II and aldosterone although in contrast to the non pregnant state there is not a close correlation between these variables In women with hypertension and proteinuria in late pregnancy renin angiotensin II and aldosterone levels are suppressed although apart from angiotensin II often still above the normal non pregnant range This suggests that the renin angiotensin aldosterone system does not play a direct pathogenic role in hypertension of pregnancy although Gordon and associates proposed that increases in the renin angiotensin aldosterone system appropriate to normal pregnancy may aggravate established pre eclampsia by failing to decline in late pregnancy

Hypertension and the oral contraceptive A small but definite rise in blood pressure occurs in most women taking estrogen/progestogen oral contraceptives and rarely severe hypertension may occur The mechanism for this blood pressure increase is uncertain Oral contraceptives produce an increase in plasma renin substrate and a fall in plasma renin concentration with a variable change in plasma angiotensin II Plasma aldosterone is not consistently increased and Weir and colleagues were unable to show a correlation between blood pressure and concurrent plasma measurements of renin renin substrate angiotensin II aldosterone cortisol or DOC nor was angiotensin II disproportionately high in relation to exchangeable sodium As yet there is no convincing evidence that changes in the renin angiotensin aldosterone system are responsible for the blood pressure rise induced by oral contraceptives

Hypertension with excess of a minderalocorticoid other than aldosterone

11 Deoxycorticosterone Brown and associates described persistently elevated plasma deoxycorticosterone (DOC) levels in six of 21 patients with hypertension low plasma renin and normal plasma aldosterone and 11 hydroxycorticosteroids Hypokalemia was observed in five Oddie and colleagues reported moderately raised plasma DOC concentrations in three of 14 patients with essential hypertension Cope and Loizou reported increased DOC excretion in five of seven patients with hypertension and hypokalemia although aldosterone excretion was also increased in one and another had a pancreatic carcinoma with an associated ectopic ACTH syndrome Others have reported normal secretion rates or plasma levels of DOC in essential hypertension

Hypertension with DOC excess has also been reported in association with an adrenocortical carcinoma

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c	Glucocorticoid remedial hyperaldosteronism
d	Adrenocortical carcinoma
e	Hyperaldosteronism associated with ovarian tumors
2	*Aldosterone excess with high plasma renin (secondary hyperaldosteronism)*
a	Benzothiadiazine diuretics
b	Renal artery stenosis and unilateral renal diseases
c	Malignant phase hypertension
d	Chronic bilateral renal disease
e	*Renin secreting renal tumor*
f	Congenital hyperaldosteronism
g	Hypertensive disease of pregnancy
3	*Non aldosterone mineralocorticoid excess*
a	Deoxycorticosterone
b	18 hydroxy deoxycorticosterone
c	Corticosterone
d	16 β hydroxydehydroepiandrosterone
e	Abnormalities of corticosteroid synthesis
f	Cushing syndrome
g	Licorice and carbenoxolone induced hypertension
4	*Low renin essential hypertension* (mineralocorticoid excess unproved— see text)

another cause is suspected diuretic treatment should be stopped and the patient then reassessed In view of the findings of Relman,[5] diuretics should be omitted for at least three weeks before investigation

Hyperaldosteronism with renal artery stenosis Many cases of renal artery stenosis especially those with malignant phase hypertension, are associated with elevated levels of renin angiotensin II and aldosterone [4 10] It has been postulated that the affected kidney receives an inappropriate signal for renin release [4] The resultant high levels of angiotensin II stimulate aldosterone secretion favoring sodium retention However the raised arterial pressure provokes a natriuresis from the unaffected kidney and the increased levels of angiotensin II may cause further sodium loss from both the post stenotic and unaffected sides [11] Total exchangeable and serum sodium may be reduced [12] Surgical relief of the stenosis often corrects both the hypertension and the biochemical abnormalities [3 4]

Hyperaldosteronism with malignant phase hypertension Malignant phase hypertension in the absence of a demonstrable renal or renovascular lesion is also often associated with high circulating levels of renin, angiotensin II and aldosterone [3 4 10 11 13] It may be that intrarenal arterial or arteriolar lesions resulting from malignant phase hypertension produce an effect on renin secretion similar to that found in renal artery stenosis certainly plasma angiotensin II levels are usually high in relation to total exchangeable sodium [16] Adequate control of the hypertension permits those lesions to heal and the elevated levels of renin angiotensin, and aldosterone may then revert to normal [4]

Increased angiotensin II levels as such are unlikely to produce the malignant phase Plasma angiotensin II is sometimes normal [13] malignant hypertension can occur in the rat when renin is sub normal [9] and indeed in man low renin hyperaldosteronism may be associated with malignant phase hypertension [4]

Hyperaldosteronism in chronic renal failure In the majority of patients undergoing regular hemodialysis for chronic renal failure blood pressure is controlled by removing sodium and water at dialysis and by restricting sodium and water intake between dialyses In a minority these measures are ineffective and severe intractable hypertension develops associated with high levels of renin angiotensin II and aldosterone [15] Removal of sodium and water at dialysis fails to control the blood pressure and results in yet higher levels of renin and angiotensin, disproportionately high in relation to exchangeable sodium [4] It may be that in this minority the grossly diseased kidneys provide an inappropriate signal for renin release Bilateral nephrectomy is followed by a rapid fall in renin and angiotensin levels and blood pressure thereafter is usually readily controlled Further evidence of the direct role of the renin-angiotensin system in maintaining hypertension in these patients is illustrated by the prompt and sustained fall of blood pressure produced during infusion of the angiotensin II antagonist saralasin [4 18]

Hypertension with a renin secreting renal tumor A number of cases of hypertension and secondary hyperaldosteronism associated with renin secreting renal tumors have now been described [4 11] Patients usually present with severe hypertension and hypokalemia High circulating levels of renin angiotensin and aldos

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   g Hypertensive disease of pregnancy
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   b 18 hydroxy deoxycorticosterone
   c Corticosterone
   d 16 β hydroxydehydroepiandrosterone
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are plasma and extracellular fluid volumes[20] Earlier reports of an increase in exchangeable sodium[58] and extracellular fluid volume[1] have been challenged[3] Furthermore there is no evidence of a bimodal distribution of plasma concentrations of renin[0] or of angiotensin II[1,2] in essential hypertension suggesting that the low renin state forms a part of a continuum in hypertension rather than a distinct diagnostic entity

In summary the hypothesis that mineralocorticoid excess is the cause of most or all cases of low renin hypertension is as yet unproved[1,7] An alternative possibility is that plasma renin falls as a result of renal adaption to long term hypertension possibly because of increased renal vascular resistance with an increase in filtration fraction[0] This hypothesis is supported by observations that plasma renin concentration is inversely related to age in patients with essential hypertension and that the normal rise in plasma renin concentration following intravenous furosemide is suppressed in hypertensive patients both with normal renin and low renin levels[7]

Grim[8] proposed that normal aldosterone levels are inappropriately high in relation to renin in such patients and suggested that low renin hypertension represents an early form of primary hyperaldosteronism Adrenal abnormalities including adenomas have been described in some patients However as stated total exchangeable sodium[9] extracellular and plasma volumes are normal in this group and we have shown that plasma aldosterone is usually suppressed by sodium loading in contrast to primary hyperaldosteronism with or without adenoma

Part II Primary hyperaldosteronism Differentiation of sub groups within the syndrome

As discussed hypertension with secondary hyperaldosteronism is distinguished from primary hyperaldosteronism by measurements of renin and angiotensin II in plasma Furthermore both an excess of mineralocorticoid other than aldosterone and low renin essential hypertension are associated with normal (or low) aldosterone values However when aldosterone excess is associated with low levels of renin and angiotensin II it remains necessary to distinguish the various forms of primary hyperaldosteronism (Table I) to facilitate rational treatment

Rare causes such as glucocorticoid remediable hyperaldosteronism and aldosterone excess associated with an adrenocortical or ovarian carcinoma must be identified However the main diagnostic problem is in differentiating the two more common forms a unilateral adrenocortical adenoma and bilateral hyperplasia of the zona glomerulosa

Glucocorticoid remediable hyperaldosteronism A number of patients have been described with hypertension hypokalemia hyperaldosteronism and low plasma renin in whom all the abnormalities were reversed by glucocorticoids[11,11] Such cases may be familial[1,11] and adrenal exploration has revealed adrenocortical hyperplasia without tumor[11,11] The cause of this abnormality remains unknown[11,5] Dexamethasone in small dosage often reversed all abnormalities within two weeks[11,111] although longer periods of treatment may be required[11]

Blood pressure and plasma electrolytes were unchanged in all of 19 patients in our series given dexamethasone for two weeks[2] However a trial of glucocorticoid suppression seems mandatory in all patients with primary hyperaldosteronism especially those in whom a tumor is not identified

Hyperaldosteronism associated with an adrenocortical carcinoma or an ovarian tumor Excessive aldosterone production by an adrenocortical carcinoma is a rare cause of primary hyperaldosteronism Early recognition is important particularly when conservative management is being considered Such cases usually show characteristic features to alert the physician[1,11] Fever severe muscle weakness and abdominal pain are common An abdominal tumor may be palpable or displace a kidney on pyelography or arteriography Excessive secretion of adrenocorticoids other than aldosterone may occur and increased urinary excretion of 17 oxogenic and/or 17 oxosteroids is usual although not invariable[6,1,3,2]

Two patients with hyperaldosteronism associated with an ovarian tumor have been reported The adrenal glands appeared normal in each but aldosterone was extracted from the tumor tissue One was a 9 year old girl with precocious puberty in whom a Sertoli cell tumor was found The other presented with a widely metastasizing arrhenoblastoma plasma levels of 17β oestradiol and testosterone were also elevated

apparently isolated corticosterone excess[63] This patient presented with hypertension hypernatremia hypokalemia and edema and an adrenocortical carcinoma was found at operation Plasma concentrations of aldosterone and cortisol were normal but plasma corticosterone was grossly raised Plasma DOC was not measured

16β hydroxydehydroepiandrosterone (16β OH DHEA) Recently raised levels of urinary 16β OH dehydroepiandrosterone were described in patients with low renin hypertension[64] This steroid was reported to have mineralocorticoid activity which, in the rat, was blocked by spironolactone[64] However, a recent report[182] has failed to confirm elevated plasma levels of this compound in low renin essential hypertension

Congenital abnormalities of corticosteroid synthesis Hypertension associated with mineralocorticoid excess occurs with 17α hydroxylase and 11β hydroxylase deficiencies, but is not usually a feature of the commoner 21 hydroxylase abnormality The raised blood pressure in such patients can be lowered towards normal by treatment with dexamethasone

17α hydroxylase deficiency This usually presents with hypertension and hypokalemia which in females is associated with primary amenorrhea and in males with pseudohermaphroditism It is associated with relative cortisol deficiency excessive deoxycorticosterone and corticosterone due to high ACTH levels, hypoaldosteronism and low plasma renin[65, 70] In a case recently studied by us[183, 184] dexamethasone treatment suppressed the elevated ACTH and returned the enhanced levels of ACTH dependent mineralocorticoids to normal Expanded exchangeable sodium fell and contracted exchangeable potassium expanded, while hypertension was relieved Subnormal plasma renin angiotensin II and aldosterone rose into their normal ranges

11b hydroxylase deficiency This condition usually presents with hypertension and virilism There is impaired formation of cortisol corticosterone and aldosterone with deoxycorticosterone excess[71, 72]

Cushing s syndrome Hypokalemic alkalosis may occur in Cushing s syndrome of various aetiologies[73, 74] while plasma renin is occasionally suppressed[74, 75] Aldosterone production is usually normal or decreased[73, 76, 77, 185] Christy and Laragh[73] reported that plasma cortisol is significantly higher in those with hypokalemia compared with normokalemic patients and postulated that the hypokalemic alkalosis is caused by higher cortisol secretion rates However, in addition to the cortisol excess, increased production and plasma levels of corticosterone and deoxycorticosterone may occur, especially associated with adrenal carcinoma or an ectopic source of ACTH[56, 57, 60, 76, 9]

Licorice and carbenoxolone induced hypertension Licorice contains glycyrrhizic acid which has a mineralocorticoid effect Consumption of large quantities of licorice containing substances may lead to hypertension, sodium retention, hypokalemic alkalosis and suppression of renin and aldosterone[80, 85, 186] These abnormalities are corrected by stopping licorice ingestion Carbenoxolone sodium is another derivative of glycyrrhetinic acid Similar abnormalities may occur when this drug is taken to aid gastric ulcer healing[3, 86, 87]

Low renin essential hypertension Some 25 per cent of patients with apparently essential hypertension have suppressed levels of plasma renin[88, 89] and it has been suggested that these patients may have an excess of an as yet unidentified mineralocorticoid which leads to renin suppression and hypertension Elevated levels of deoxycorticosterone and 18 OH deoxycorticosterone have been shown in a minority of such patients

Particular circumstances certainly suggest the presence of mineralocorticoid excess Patients with low renin essential hypertension have a lower salivary sodium/potassium ratio than do patients with hypertension associated with normal plasma renin[90] They may show a more marked hypotensive response to the mineralocorticoid antagonist spironolactone than do those with normal renin values[91, 93] as well as a more marked hypotensive response to the adrenal inhibitor aminoglutethimide[58] These observations have been widely interpreted to indicate mineralocorticoid excess although other diuretics also seem more effective in lowering blood pressure in the low renin group[94, 96] Spark and colleagues[97] reported a greater hypotensive response to spironolactone than to a thiazide diuretic, an observation previously described in primary hyperaldosteronism[98] In contrast to primary hyperaldosteronism however total exchangeable sodium is normal in low renin essential hypertension[8] as

nine cases A definitive pathological diagnosis was not reached in three patients who were excluded from the remainder of the analysis

Mean plasma concentrations of aldosterone and tCO were significantly higher in the adenoma group while mean concentrations of potassium and renin were significantly lower compared with patients without adenoma (Fig 1) Mean plasma sodium was also higher while mean age and mean systolic and diastolic blood pressures were lower in the adenoma group but these differences did not reach statistical significance However individual values for each of these variables overlapped (Fig 1) and straightforward analysis of preoperative data did not always enable a confident prediction of adrenal pathology When the statistical technique of quadric analysis was applied complete separation of the adenoma and non adenoma groups was achieved (Fig 2)

The technique of quadric analysis was also applied to other published series of patients with primary hyperaldosteronism [5] again retrospectively Quadrics were circumscribed about known adenoma and non adenoma groups in each series and the degree of separation was examined Where quadrics overlapped patients we classified by likelihood ratio technique With only two exceptions complete separation of the adenoma and non adenoma patients in each series was achieved However when the data from these patients were examined relative to the quadrics of the original series [4] much less satisfactory separation was achieved This illustrated that classification of individual patients with reference to quadrics established at another center is open to considerable error unless care is taken to standardize the biochemical measurements made in the laboratories concerned

Since our original report [4] we have investigated and surgically explored a further 24 patients with primary hyperaldosteronism A unilateral adenoma was found in 20 while in four further cases a tumor was not found the adrenal glands showing bilateral hyperplasia in each (Table II) Using quadric analysis adenoma was correctly predicted before operation in each of the 20 cases Bilateral hyperplasia was correctly predicted in three of four cases but an adenoma was incorrectly predicted in the fourth

Thus adrenal pathology has been correctly predicted before operation in 23 of 24 cases The

Table II Results of quadric analysis used prospectively

Patient initials	*Pathological diagnosis*	*Quadric analysis prediction*	*Prediction odds*
E B	Adenoma	Adenoma	89 5 1
F D	Adenoma	Adenoma	307 2 1
F G	Adenoma	Ad noma	57 3 1
M F	Adenoma	Adenoma	6 2 1
W G	Adenoma	Adenoma	521 7 1
M G	Adenoma	Adenoma	172 5 1
M H	Adenoma	Adenoma	10 5 1
G H	Adenoma	Adenoma	18 1
T H	Adenoma	Adenoma	48 1
F J	Adenoma	Adenoma	1,84 1
J M	Adenoma	Adenoma	15 5 1
J O R	Adenoma	Adenoma	27 4 1
J R	Adenoma	Adenoma	143 1
L S	Adenoma	Adenoma	68 1
M S	Adenoma	Adenoma	2 9 1
M G	Adenoma	Adenoma	22 8 1
E T	Adenoma	Adenoma	60 8 1
A McD	Adenoma	Adenoma	134 4 1
H K	Adenoma	Adenoma	49 7 1
G Q	Adenoma	Adenoma	16 3 1
J W	Non adenoma	Adenoma	56 1
M K	Non adenoma	Non adenoma	2 3 1
A McP	Non adenoma	Non adenoma	18 3 1
G T	Non adenoma	Non adenoma	194 1

scarcity of patients without adenoma in this prospective group reflects our current bias against surgery in these patients [2]

2 *Other statistical techniques* Recently Luetscher and colleagues[1] used computer aided multiple logistic analysis of plasma potassium plasma renin and urinary aldosterone to separate adenoma and non adenoma patients with primary hyperaldosteronism By this means seven patients with an aldosterone producing adenoma were separated from four with bilateral adrenocortical hyperplasia Thereafter adrenal pathology was correctly predicted in a further five cases

Biglieri and colleagues [1,1] separated patients with and without adenoma by plotting basal recumbent plasma renin concentration against aldosterone excretion after sodium loading Using linear discriminant analysis these workers correctly predicted adrenal pathology in a further 13 cases

3 *Sodium loading with DOCA or fludrocortisone* Biglieri and associates[1] described the effects of sodium loading on aldosterone excre

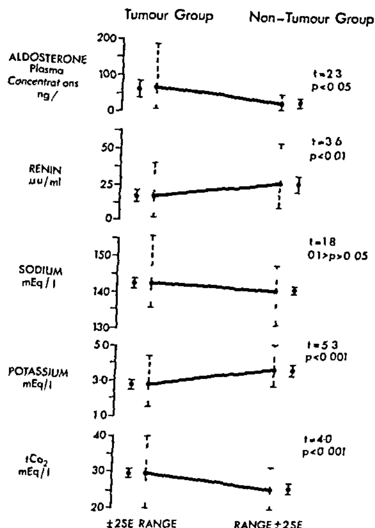


Fig 1 Comparison of biochemical variables in adenoma and non adenoma patients with primary hyperaldosteronism Renin is expressed in terms of the International Reference Standard

Differentiation of adenoma from bilateral hyperplasia A large number of methods have been described for preoperative differentiation of patients with a unilateral adenoma from those with bilateral hyperplasia of the zona glomerulosa These include statistical techniques such as quadric *analysis*[127, 128] *multiple logistic analysis*[1, 9] and linear discriminant analysis[130, 131] Other methods include sodium loading with deoxy corticosterone[13] or fludrocortisone[110, 113] comparison of *postural*[134, 135] *and diurnal*[133, 13] *changes in* plasma aldosterone and comparison of change occurring during treatment with spironolactone[135, 14] The adrenal glands have been examined by venography[139, 151] ultrasound,[151] and scintillation scanning[15, 153] while the aldosterone concentration in the effluent of each adrenal gland has been compared[113, 14, 150, 154] These various methods are discussed in detail below

1 Quadric analysis The statistical technique of quadric analysis has been described in detail

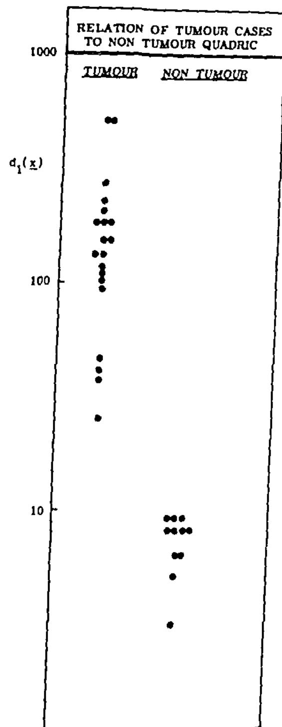


Fig 2 Differentiation of adenoma and non adenoma patients with primary hyperaldosteronism by quadric analysis Retrospective series (see text)

elsewhere[1, 7, 128] The essence of the method is to combine data from individual patients and by so characterizing them to increase discrimination between patients of different pathological groups We initially reviewed a group of 34 patients with hypertension *aldosterone excess and low plasma* renin concentration[1, 7] Twenty patients had a unilateral adrenocortical adenoma while no tumor was identified in eleven the adrenal glands *showing hyperplasia of the zona glomerulosa in*

nine cases. A definitive pathological diagnosis was not reached in three patients who were excluded from the remainder of the analysis.

Mean plasma concentrations of aldosterone and tCO were significantly higher in the adenoma group while mean concentrations of potassium and renin were significantly lower compared with patients without adenoma (Fig. 1). Mean plasma sodium was also higher while mean age and mean systolic and diastolic blood pressures were lower in the adenoma group but these differences did not reach statistical significance. However, individual values for each of these variables overlapped (Fig. 1) and straightforward analysis of preoperative data did not always enable a confident prediction of adrenal pathology. When the statistical technique of quadric analysis was applied complete separation of the adenoma and non adenoma groups was achieved (Fig. 2).

The technique of quadric analysis was also applied to other published series of patients with primary hyperaldosteronism was again retrospectively. Quadrics were circumscribed about known adenoma and non adenoma groups in each series and the degree of separation was examined. Where quadrics overlapped patients we classified by likelihood ratio technique. With only two exceptions complete separation of the adenoma and non adenoma patients in each series was achieved. However, when the data from these patients were examined relative to the quadrics of the original series much less satisfactory separation was achieved. This illustrated that classification of individual patients with reference to quadrics established at another center is open to considerable error unless care is taken to standardize the biochemical measurements made in the laboratories concerned.

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Patient initials	*Pathological diagnosis*	*Quadric analysis prediction*	*Prediction odds*
E B	Adenoma	Adenoma	89.5 1
F D	Adenoma	Adenoma	30[illegible] 1
F G	Adenoma	Adenoma	5.3 1
M F	Adenoma	Adenoma	6[illegible] 1
W G	Adenoma	Adenoma	[illegible]17 1
M G	Adenoma	Adenoma	1 2 1
M H	Adenoma	Adenoma	10.5 1
G H	Adenoma	Adenoma	18 1
T H	Adenoma	Adenoma	48 1
F J	Adenoma	Adenoma	1 84 1
J M	Adenoma	Adenoma	15.5 1
J O R	Adenoma	Adenoma	2[illegible]4 1
J R	Adenoma	Adenoma	143 1
L S	Adenoma	Adenoma	686 1
M S	Adenoma	Adenoma	2.9 1
M G	Adenoma	Adenoma	22.8 1
E T	Adenoma	Adenoma	60.8 1
A McD	Adenoma	Adenoma	134.4 1
H K	Adenoma	Adenoma	49[illegible] 1
G Q	Adenoma	Adenoma	16.3 1
J W	Non adenoma	Adenoma	5[illegible] 1
M K	Non adenoma	Non adenoma	[illegible]3 1
A McP	Non adenoma	Non adenoma	18.3 1
G T	Non adenoma	Non adenoma	19.4 1

scarcity of patients without adenoma in this prospective group reflects our current bias against surgery in these patients.

2. Other statistical techniques. Recently Luetscher and colleagues[1] used computer aided *multiple logistic analysis* of plasma potassium, plasma renin and urinary aldosterone to separate adenoma and non adenoma patients with primary hyperaldosteronism. By this means seven patients with an aldosterone producing adenoma were separated from four with bilateral adrenocortical hyperplasia. Thereafter adrenal pathology was correctly predicted in a further five cases.

Biglieri and colleagues separated patients with and without adenoma by plotting basal recumbent plasma renin concentration against aldosterone excretion after sodium loading. Using linear discriminant analysis these workers correctly predicted adrenal pathology in a further 13 cases.

3. Sodium loading with DOCA or fludrocortisone. Biglieri and associates described the effects of sodium loading on aldosterone excre

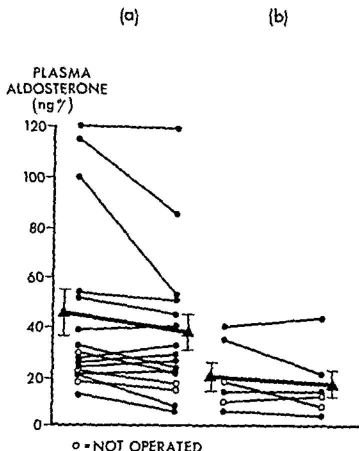


Fig 3 Plasma aldosterone before and during administration of 9α fludrocortisone in adenoma (*a*) and non adenoma (*b*) *patients with primary hyperaldosteronism Triangles with* vertical bars represent means ± S E M Open circles represent unoperated patients whose adrenal pathology was predicted by quadric analysis

tion Deoxycorticosterone acetate (DOCA) for three days failed to alter aldosterone excretion in patients with an aldosterone producing adenoma but caused suppression in normals in patients with essential and renovascular hypertension and in those with primary hyperaldosteronism in whom a tumor was not found at operation This seemed a useful maneuver for differentiating adenoma and non adenoma patients but it is now apparent that some of the latter also fail to suppress [111, 159] These workers also proposed that oral fludrocortisone (0 8 mg daily for 3 days) might distinguish primary from secondary hyper aldosteronism, as in the former aldosterone excre tion was usually *not suppressed* [135] However a slightly larger dose did cause aldosterone suppres sion in one of five patients *with an aldosterone* producing adenoma [160]

We recently described the response of plasma aldosterone to fludrocortisone (0 8 mg daily for 3 days) in 22 patients with low renin hyperaldoster onism, with and without adenoma [110] Although basal aldosterone levels were often higher in adenoma patients, there was no significant change in mean values during treatment in either group (Fig 3) Furthermore the pattern of change did not differ among individual patients an occasional response occurred in each group We also studied patients with low renin and normal renin essential hypertension and hyper tension associated with isolated deoxycorticoster one excess Although plasma aldosterone de creased markedly in most patients an occasional increase occurred in each group [110]

In our hands therefore this test was of little value in separating adenoma and non adenoma patients with primary hyperaldosteronism

4 *Basal plasma renin plotted against aldos terone after fludrocortisone* In another attempt to separate patients with primary hyperaldoste ronism, with and without an adrenocortical tumor Biglieri and associates[111] plotted basal recumbent plasma renin concentration against the aldosterone excretion rate on the third day of sodium loading with deoxycorticosterone acetate By this means they completely separated adenoma and non adenoma patients in a retros pective analysis and using these data they correctly predicted adrenal pathology in a further 13 patients

We recently reported the relationship between basal plasma renin concentration and plasma aldosterone after fludrocortisone in 22 patients with low renin hyperaldosteronism [110] The result is shown in Fig 4, no useful separation between tumor and non tumor groups was observed This study differed from that of Biglieri and colleagues in using plasma levels of aldosterone rather than urinary excretion and the differential renin assay method

5 *Plasma aldosterone postural change and diurnal variation* The normal rise in plasma aldosterone on changing from the supine to the erect position also occurs in patients in the hyper plasia group but less markedly in patients with an aldosterone producing adenoma [111, 133, 134] These differing responses to posture have been suggested as a method for distinguishing the two groups preoperatively [134, 135] Furthermore a diur nal variation in plasma aldosterone paralleling cortisol has been described in patients with an aldosterone producing adenoma but not among patients in the hyperplasia group [133] It has been suggested that ACTH controls diurnal aldoster

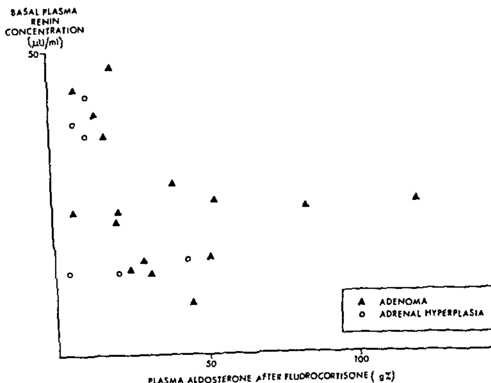


Fig 4 Basal plasma renin concentration plotted against plasma aldosterone after three days of 9α fludrocortisone in patients with primary hyperaldosteronism Triangles represent adenoma and open circles non adenoma patients

one variation in patients with adenoma but not in those with hyperplasia

These differences in plasma aldosterone between the pathological groups are of considerable interest and emphasize the importance of measuring plasma aldosterone at fixed times and under defined conditions However the value in differentiating individual patients with and without adenoma will be restricted by the exceptions that occur Occasionally plasma aldosterone may increase on assuming an erect posture in patients in the adenoma group Furthermore a fall in plasma aldosterone through the day is not invariable in patients with adenoma and may also occur in patients with hyperplasia

6 *Response to spironolactone* Spark and Melby reported a fall in blood pressure to normal during treatment with spironolactone in each of 20 patients subsequently shown to harbor an aldosterone producing adenoma Two further patients with primary hyperaldosteronism in whom a tumor was not found at operation failed to show a blood pressure response fall during spironolactone It seemed that the blood pressure response to spironolactone might prove a useful guide to adrenal pathology However in a larger series we found that a good hypotensive response to spironolactone can occur both in patients with and without adenoma [2] Thus the blood pressure response to this drug is not of practical value in differentiating adenoma and non adenoma cases

Ganguly and co workers compared changes in renin and aldosterone during spironolactone therapy in patients with primary hyperaldosteronism with and without adenoma The rise in plasma renin concentration was significantly greater in the non adenoma group Plasma aldosterone also increased substantially in two of three patients but was unchanged in the adenoma group although it was unclear whether a similar dosage was used Schambelan and associates [38] reported similar findings

We have been unable to confirm these observations We found a consistent rise in plasma renin concentration during spironolactone treatment in both adenoma and non adenoma patients and the magnitude was similar in the two groups (Fig 5)

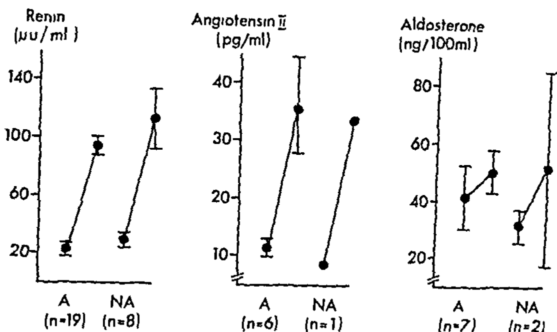


Fig 5 Changes in plasma concentrations of renin angiotensin II and aldosterone in adenoma (*A*) and non adenoma (*NA*) patients with primary hyperaldosteronism during treatment with spironolactone (mean dosage 320 mg/day in adenoma group and 260 mg/day in non adenoma group)

When measured plasma angiotensin II increased similarly (Fig 5) The changes in plasma aldosterone were more variable among seven patients with adenoma values rose in four fell in two and were unchanged in one Plasma aldosterone was measured before and during spironolactone therapy in two patients without tumor in one there was a large rise and in the other a smaller fall In our experience the renin angiotensin, and aldosterone response to spironolactone appears similar in the two pathological groups

Robertson has pointed out that the greater responses in non adenoma patients reported by others would be expected if a standard spironolactone dose was used in the two groups Patients without adenoma generally have less severe aldosterone excess so a greater correction of electrolytes and renin might occur In our experience patients without adenoma generally require a somewhat smaller dose (Fig 5)

7 *Adrenal venography and adrenal vein sampling* Localization of adrenocortical adenomata by retrograde injection of dye into the adrenal vein has been widely used[13-15] Melby and colleagues[13] lateralized aldosterone producing adenomas too small to detect on venography, by measuring aldosterone concentrations in the venous effluent of each adrenal gland Although technically difficult the value of this procedure has also been confirmed[14,15]

The results of adrenal venography and adrenal vein sampling for aldosterone measurement in some of the patients in this series have been reported[151,154] Among 14 patients with an aldosterone producing adenoma subsequently confirmed at operation the tumor was correctly identified in 11 (Fig 6) and suspected in two while catheterization was unsuccessful in the remaining patient Five further patients had bilateral adrenocortical hyperplasia a macronodule was identified on venography in one but was not distinguishable from an adenoma while in two further patients an adenoma was incorrectly suspected Thus although adrenal venography was accurate in lateralizing adenomas false positives were common among patients without tumor and a macronodule was indistinguishable from an adenoma

Measurements of aldosterone in adrenal vein plasma were also valuable in lateralizing adenomas the ratio between affected and unaffected sides ranging from 3 to 64 to 1 However aldosterone concentration did not clearly separate normal and adenoma bearing glands and bilateral samples are not always obtainable for technical reasons

The complications of adrenal venography have been stressed notably adrenal and iliac vein thrombosis and extravasation of contrast medium into the adrenal gland[161-163] Adrenal insufficiency followed venography in two of 58 patients in this series[151,154]

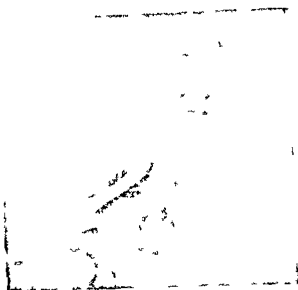


Fig 6A Left adrenal venogram in a patient with aldosterone producing adenoma



Fig 6B Left adrenal gland removed at operation from the same patient as in *Fig 6A* Note an adrenocortical adenoma at the lower pole

8 Other radiological techniques A plain abdominal film or pyelography may occasionally show renal displacement suggesting an adrenal carcinoma [1] [6] Retroperitoneal pneumography with tomograms of the adrenal area may reveal an irregularity in normal gland contour indicating the presence of an adenoma However small tumors are not identified [6] and because of the great variation in normal gland size adrenal hyperplasia can at best only be suspected Furthermore this technique carries a small but appreciable risk of air embolism [6] [69]

The adrenal glands may sometimes be seen on aortography although this is variable and aldosterone secreting adenomas usually lack sufficient vascularity to be visible Techniques for selective catheterization of the adrenal arteries have been described [3] The value of this procedure has been limited by technical difficulties by the great variation in arterial supply and by the fact that each injection permits visualization of only a portion of the gland [1] [3] However Kahn and associates successfully identified the adrenal abnormality in 19 of 20 patients with primary aldosteronism using the combined techniques of selective adrenal arteriography adrenal venography and adrenal vein plasma sampling

9 Ultrasound Ultrasound examination of the adrenal glands was undertaken in 10 patients in this series in whom an adenoma was identified at venography [13] The normal gland was not identifiable by the method used Two adenomas were located of diameters 30 and 31 mm respectively However early in the series an adenoma of diameter 35 mm was overlooked while seven tumors 10 to 25 mm in diameter were not identified Davidson and colleagues [3] concluded that tumors greater than 30 mm in diameter should be identified with currently available commercial equipment in agreement with the findings of Birnholtz [74]

10 Scintillation scanning The adrenal glands may also be visualized by scintillation scanning following intravenous I 19 iodocholesterol which they actively concentrate [7] Patients with aldosterone producing adenomas have been identified by concentration of radioactivity at the site of the tumor while a patient with bilateral hyperplasia showed diffuse adrenal uptake which unlike adenomas was suppressed by dexamethasone Recently Hogan and colleagues [5] and Conn and associates[18] differentiated patients with and without adenoma by repeated scanning without the use of dexamethasone An adrenocortical adenoma was identified by an area of increased activity in 10 of 12 patients while an

asymmetrical uptake was uncommon in patients with hyperaldosteronism presumed due to adrenal hyperplasia and in low renin essential hypertension. Two patients with aldosterone excess and an adrenal carcinoma failed to show an increased uptake in their tumor.

This procedure, as yet experimental, seems promising. Errors may occur because of uptake by related or overlying structures,[153] while the ^{131}I dose required is still large.[illegible, 153] Recently a new scanning agent, ^{131}I 6β iodomethyl 19 norcholesterol, was reported to have a higher adrenal uptake with improved images.[156]

11. Other methods. Wotman and associates[157] reported that the potassium concentration in submaxillary saliva was higher in patients with an aldosterone producing adenoma than in normals, in essential hypertension and in those with primary hyperaldosteronism associated with adrenal hyperplasia only. However, the groups studied were small and the results showed a wide scatter; it seemed likely that with larger numbers some overlap would occur. There was no difference between the groups in the potassium concentration in parotid saliva.

Measurement of electrical potential difference across rectal mucosa has been proposed as a useful screening test for mineralocorticoid excess.[158] In our experience this technique is of limited usefulness and is unlikely accurately to differentiate adenoma and non adenoma patients with aldosterone excess.[159]

Summary

Hypokalemia in a hypertensive patient is commonly diuretic induced. However, if hypokalemia persists after stopping diuretic therapy, possible mineralocorticoid excess including primary hyperaldosteronism must be considered. Hypertension with secondary hyperaldosteronism may occur with malignant phase hypertension and with renal or renovascular disease. However, secondary hyperaldosteronism is associated with raised circulating levels of renin and angiotensin II, while in primary hyperaldosteronism plasma concentrations of renin and angiotensin II are inappropriately low.

Hypertension and hypokalemia may also be associated with an excess of a mineralocorticoid other than aldosterone. Syndromes associated with an apparently isolated excess of 11 deoxycorticosterone, of 18 hydroxy 11 deoxycorticosterone and of corticosterone have been described. Plasma renin may be suppressed as in primary hyperaldosteronism, but aldosterone values are normal or low. Hypertension, hypokalemia and renin suppression may also occur in Cushing's syndrome, associated with abnormalities of corticosteroid synthesis and during ingestion of licorice containing drugs. Again, aldosterone values are normal or low.

Once the diagnosis of primary hyperaldosteronism has been confirmed, the rare cases of glucocorticoid remediable hyperaldosteronism and hyperaldosteronism associated with adrenal or ovarian carcinoma must be excluded. Thereafter, it is necessary to distinguish between the two commonest forms, a unilateral adrenocortical adenoma and bilateral hyperplasia of the zona glomerulosa. The statistical technique of quadric analysis used prospectively has correctly predicted adrenal pathology in 23 of 24 patients. Other methods for differentiating the two groups include comparisons of aldosterone response to sodium loading, comparison of postural and diurnal changes in plasma aldosterone, adrenal venography, and examination of the adrenal glands by ultrasound and by scintillation scanning.

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Radionuclides in the assessment of myocardial infarction

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Radionuclides in Cardiology have been used mainly for detection of myocardial infarction and assessment of left ventricular function [1] The need for improved detection of myocardial infarction is related to the lack of sensitivity and specificity of the ECG or plasma enzymes in certain clinical conditions Diagnosis of infarction after cardiac surgery is particularly troublesome since even creatine phosphokinase isoenzymes specific for myocardial damage are consistently elevated as a result of the iatrogenic injury The recent interest in protection of ischemic myocardium[4] requires measurement of infarct size and several studies suggest that quantification of infarct images may be possible [7 8] which has intensified the search for more appropriate radionuclides

Four categories of radionuclides have been utilized to identify zones of ischemia or infarction as areas of decreased activity or cold spots (1) Potassium analogs (^{43}K $^{?}$Cs $^{?}$Rb and more recently ^{201}Tl) [9 ?] (2) metabolic substrates (labeled free fatty acids ^{13}NH (3) inert gases (^{81}Kr ^{133}Xe) [?] and (4) labeled microspheres or macroaggregates [8 9] However radionuclides which accumulate in areas of infarction (hot spots)[?] offer some advantages over those which localize in normal tissue (cold spots) To date radiopharmaceuticals which produce cold spots cannot distinguish acute myocardial infarction from scar tissue old infarction or ischemia [11 14] Accordingly this review will deal primarily with those agents which are taken up in the area of infarction

Historically the first studies to delineate myocardial infarction by a radionuclide accumulating in necrotic tissue utilized mercurial compounds [10] Poor resolution and radiation risks precluded their extensive use clinically [21] Subsequently the serendipitous discovery that bone seeking radionuclides accumulate in myocardial infarcts initiated the widespread use of technetium labeled compounds for infarct imaging [22]

The basis of a positive image is dependent on several factors (1) the ratio of radioactivity in infarcted compared to normal myocardium which should generally be at least 4 1 (2) the ratio of radioactivity in myocardium to that of surrounding structures (ribs liver etc) (3) the size of the infarct and (4) the distribution and density of cell death (although the same number of myocardial cells may be necrotic in subendocardial as in transmural infarctions the latter is more easily visualized scintigraphically because of the localization of counts in one area)

Mercurial compounds

Mercurochrome has long been known to stain necrotic tissue and fluoresce under ultraviolet light [23] Much of the early work in myocardial infarct imaging was performed using compounds labeled with radioactive mercury because of their stability and accumulation in necrotic tissue [1] The first attempts to demonstrate radionuclide

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labeling of leukocytes with ^{111}In 8 hydroxyquinoline[33] This was accomplished without alterations in white blood cell viability or function When labeled leukocytes are administered to animals with experimental infarction images of the infarct can be obtained in dogs 24 hours after coronary occlusion Forty eight hours after infarction an increased number of counts were detected in the infarct zone compared to the normal myocardium Ratios of radioactivity of infarct compared to normal myocardium were 23 1

Tetracycline

Since the mercurial compounds produce infarct images with poor resolution and since radiopharmaceuticals which accumulate in infarcts as a result of inflammation lack specificity investigators initiated studies with technetium–labeled tetracycline designed to improve sensitivity and specificity Like the mercurial compounds tetracycline fluoresces and accumulates in myocardial tissue undergoing necrosis[5] Immediately after intravenous administration tetracycline produces a yellow fluorescence in normal heart muscle but not in necrotic tissue However within the next three hours the intensity of fluorescence increases around the infarct border and is absent from normal tissue The mechanism of accumulation of ^{99m}Tc(Sn) tetracycline is thought to be related to binding of the tracer to protein in nucleic acids in necrotic myocardial cells Its accumulation appears to be influenced by free calcium accumulation in necrotic myocardium–a mechanism postulated for other radiopharmaceuticals as well[4] After three to four days fluorescence is seen only in the margin of the infarct and by seven days clumps of tracer are noted throughout the infarct With administration of 10 to 15 mCi of ^{99m}Tc(Sn) tetracycline intravenously 4 to 24 hours after acute myocardial infarction accumulation is primarily in the liver kidneys and gall bladder Four hours after infarction only one of four dogs had a scintigraphically demonstrable infarct By 24 hours however ratios of radioactivity in infarcts compared to normal myocardium ranged from 5 9 to 8 4 1 Hemorrhagic infarcts were more readily demonstrable by labeled tetracycline[35]

Early studies in patients' demonstrated that each of 14 patients with acute myocardial infarction had positive ^{99m}Tc(Sn) tetracycline images if injected 24 hours after infarction and imaged 24 hours after injection All nine patients without acute infarction had negative images including several patients with old infarction Localization of infarction determined scintigraphically was concordant with electrocardiographic localization Also the correlation of infarct size (measured by peak total CPK) with images categorized as having large moderate or small infarcts scintigraphically was good ($r = 0\ 84$)

The sensitivity and specificity of ^{99m}Tc(Sn) tetracycline myocardial imaging is less impressive in other studies[36] Only 12 of 25 true positive and six of 11 true negative images were reported in one study[5] Other difficulties precluding the widespread clinical utility of ^{99m}Tc(Sn) tetracycline myocardial imaging include the following (1) the 24 hour delay from infarct to image precludes early infarct diagnosis (2) uptake of the tracer by the liver makes the accurate diagnosis of diaphragmatic infarction difficult (3) relatively small ratios of activity in infarcts compared to normal myocardium account for poor delineation of the infarct zone Hence ^{99m}Tc(Sn) tetracycline has not become a frequently used method of infarct imaging

^{99m}Technetium glucoheptonate

A major difficulty with most imaging agents in diagnosing acute myocardial infarction has been the delay in the production of an abnormal image Circumventing this problem by finding a radionuclide designed to permit early imaging would be of great importance One agent that appears to offer promise in detecting infarction sooner is ^{99m}Tc glucoheptonate When this radionuclide was administered to nine dogs four hours after coronary occlusion the ratio of activity in infarcts compared to normal myocardium was 20 1 Concentration of the radionuclide in infarcts was somewhat dependent on blood flow since the greatest number of counts occurred when perfusion was 20 to 40 per cent of normal Early imaging was not significantly encumbered by overlay of radioactivity in skeletal structures or cardiac blood pool and ratios of radioactivity in infarcts compared to normal tissue were better than those seen with ^{99m}Tc(Sn) tetracycline but similar to those observed with ^{99m}Tc(Sn) pyrophosphate[32, 7]

In one study of 27 patients with chest pain ^{99m}Tc glucoheptonate was administered two to 48

accumulation in experimental myocardial infarcts *in vivo* were performed in 1962 using ^{203}Hg chlormerodrin[10] Fifteen of 16 dogs with coronary occlusions were shown to have abnormal scintigrams with a preponderance of counts in ischemic and necrotic myocardium compared with normal myocardium by direct counting of histologic specimens Imaging of myocardial infarcts *in vitro* in pigs also demonstrated accumulation of ^{203}Hg chlormerodrin as early as 12 to 24 hours after infarction but with optimal results at three to five days after infarction Images were normal by 9 to 12 days[24] Of even greater interest was the finding that coronary reperfusion was not necessary for accumulation of mercurial compounds in infarcts[25] Studies in patients, however, have been disappointing[6] Only three of 13 patients with myocardial infarctions were successfully imaged with ^{203}Hg chlormerodrin four to eight days post infarction In dogs it was necessary to administer 700 μCi but the 47 day half life of ^{203}Hg and high radiation exposure to the liver and kidney precluded the use of high doses in humans Thus the amount of activity accumulated in the myocardial infarcts was suboptimal for image production Other mercurial compounds however, have been shown to accumulate more avidly in myocardial infarcts[27] For example ^{203}Hg hydroxy mercury 4 5 dibromofluorescein has a ratio of activity in infarcts compared to normal myocardium of 100 1 while ^{203}Hg chlormerodrin has a ratio of only 6 1 Although other radiopharmaceuticals have more recently taken the place of mercurial compounds in clinical use these radionuclides were instrumental in establishing that (1) tracers do accumulate in myocardial infarcts (2) they can be detected externally, and (3) accumulation occurs despite total occlusion of a coronary artery

Iodinated compounds

Some early studies reported the accumulation of ^{131}I in myocardial infarcts[28] One study of 23 patients with acute myocardial infarction reported a 20 per cent greater number of counts localized over the left side of the chest when compared to the right side after oral administration of 50 to 200 μCi of Na^{131}I Seven days after infarction however postmortem data revealed a ratio of radioactivity in infarcts compared to normal myocardium of only 1 7 1[4] Subsequent studies demonstrated that the left precordial activity probably represented ^{131}I concentration in gastric secretions persisting in the stomach due to delayed gastric emptying seen in patients with recent myocardial infarctions[9]

Gallium citrate

After it was recognized that mercurial radionuclides would not be beneficial in the clinical setting of infarct imaging investigators turned to agents such as gallium citrate ^{67}Gallium citrate is a radiopharmaceutical which accumulates in areas of inflammation and in certain tumors[30] Since this radiopharmaceutical accumulates in white blood cells which are known to migrate to the periphery of acute infarctions it seemed likely that ^{67}Gallium citrate would accumulate in regions of myocardial necrosis When 3 to 4 mCi of ^{67}Gallium citrate were administered intravenously two days after transient occlusion of the left anterior descending coronary artery, accumulation of the radionuclide was noted in dogs with infarction (prolonged occlusion) but not with transient ischemia (less than 20 minute occlusions) Furthermore, *in vivo* and *in vitro* studies demonstrated a good correlation between the intensity of ^{67}Gallium uptake and the number of leukocytes seen histologically in the infarct zone as well as with the extent of myocardial CPK depletion[31] However, ^{67}Gallium myocardial imaging has not been shown to be useful clinically Since the ratio of radioactivity in infarcts compared to normal myocardium is relatively small compared to other radionuclides, one would expect rather poor sensitivity[32] In one study, only five of eight patients with myocardial infarction demonstrated an abnormal image It should be emphasized that ^{67}Gallium detects areas of inflammation and is, therefore not specific for infarction Hence, other disorders such as pericarditis might also be associated with an abnormal image Accumulation of gallium by the liver makes recognition of diaphragmatic infarctions difficult In addition images do not become abnormal for several days, precluding early detection of infarction Furthermore since images remain abnormal for at least three weeks serial imaging is impossible[31]

Indium labeled leukocytes

Further attempts to take advantage of the migration of leukocytes into infarcts for the purposes of myocardial imaging employed the

and specificity of ^{99m}Tc(Sn) pyrophosphate in detecting acute myocardial infarction were excellent unless images were obtained more than seven days after infarction[20] Localization of infarction by imaging compared with electrocardiograms was very good

One large study of 101 patients with myocardial infarction demonstrated 96 abnormal images The five patients with false negative images were all scanned more than seven days after infarction Ninety two of 101 patients without infarction had negative images Of the remaining nine positive images seven patients were thought to have unstable angina A second study of 165 patients showed that 85 per cent with infarction based on electrocardiograms and elevated plasma MB CPK activity had positive images There was a 7 per cent false positive rate some of whom represented patients arriving in the Coronary Care Unit several days after infarction at a time when cardiac enzymes had returned to baseline but when images were still abnormal In other studies [9] ^{m}Tc(Sn) pyrophosphate detected 17 of 17 true positives and seven of 10 true negatives This tracer appears to display the greatest sensitivity and specificity and the highest quality images when compared to other technetium labeled compounds [4]

^{m}Tc(Sn) pyrophosphate images are also capable of detecting acute subendocardial infarction Each of 17 patients with subendocardial infarction diagnosed by conventional diagnostic criteria had abnormal images which were either localized or faint diffuse abnormalities This latter type of abnormality has been noted to be characteristic of non transmural infarctions [5]

Despite experimental data showing that transient coronary occlusions do not produce abnormal images and that the location of accumulation of ^{m}Tc(Sn) pyrophosphate corresponds to the location of greatest calcium deposition (known to occur only in necrotic myocardium) the specificity of this radionuclide for detection of infarction remains controversial Patients with unstable angina in the absence of injury appear to exhibit abnormal images Evidence suggesting that ischemia per se is not associated with abnormal images is mounting Fetal mouse hearts which were reversibly damaged by perfusion with solutions containing no glucose or oxygen for 24 hours at 37 C exhibited very little ^{99m}Tc(Sn) pyrophosphate accumulation In contrast irreversible damage with hypoxia and hypoglycemia at 42° C was associated with 152 per cent greater activity at 24 hours compared with that noted after one hour [4] Furthermore patients undergoing maximal exercise stress tests do not exhibit abnormal ^{99m}Tc(Sn) pyrophosphate images [7] Thus these images appear to be specific for infarction in this setting In studies in our own laboratory (unpublished data) in patients with unstable angina in whom infarction is excluded by normal plasma MB CPK abnormal images were generally not seen even if the tracer was injected at the time of chest pain or 24 hours later These data suggest that many of the patients with positive images and a history of unstable angina actually have subendocardial infarctions

Numerous causes of false positive ^{m}Tc(Sn) pyrophosphate images have been reported including left ventricular aneurysms [4] ventriculotomy scars from sump drains and calcified heart valves [50] Whether or not images are abnormal in the presence of calcified valves may be related to the rate of calcium turnover degree of calcium deposition or blood supply to paravalvular tissue Closed chest massage [5] and direct countershock in animals[5] and in patients[51] have been shown to be associated with abnormal images This may be related to cardiac trauma or deposition of the radionuclide in necrotic chest wall muscles

As previously mentioned diffusely positive ^{m}Tc(Sn) pyrophosphate images have been reported primarily in patients with unstable angina or subendocardial infarction [5] However the *specificity of the diffusely positive image has been* questioned In preliminary studies diffusely abnormal images were observed in some normal subjects [5] Subsequent data from normal subjects given ^{99m}Tc(Sn) pyrophosphate intravenously revealed that a delay in clearance of the tracer from the cardiac blood pool in some patients was responsible for production of a diffusely positive image These findings emphasize the need for delayed images (two hours) after injection of the tracer before a diffuse image is considered abnormal [7]

Diagnosis of acute myocardial infarction at the time of cardiac surgery is frequently difficult The conventional indices of infarction (history cardiac enzymes and electrocardiograms) may lack the usual specificity in the setting of recent surgery [56] In a study of 50 patients undergoing

hours after chest pain and 12 of 15 patients with acute infarction exhibited abnormal images Several false positive images were reported Scintigraphically estimated infarct size correlated well with peak total CPK (r = 0 77)[39] In another study, ^{99m}Tc glucoheptonate detected only three of 13 true positives and two of two true negatives[36] Thus, despite some encouraging experimental results, drawbacks of poor resolution, and poor sensitivity make ^{99m}Tc glucoheptonate infarct imaging less beneficial than other tracers presently in use

Bone seeking radionuclides

Introduction Bone seeking tracers were noted to accumulate in zones of acute myocardial infarction during routine bone scans[20] Subsequently phosphate compounds labeled with technetium were found to be excellent indicators of acute myocardial necrosis, and are presently used extensively in many Coronary Care Units

^{99m}Tc(Sn) pyrophosphate Some of the earliest studies utilizing bone seeking radionuclides were performed in dogs with experimental infarction given ^{99m}Tc(Sn) pyrophosphate This tracer is a commonly used bone scanning agent Technetium 99m with its 140 keV gamma rays and its short half life is well suited for nuclear medicine instrumentation

The mechanism of accumulation of ^{99m}Tc(Sn) pyrophosphate in acute infarction has not been unequivocally established Electron dense deposits of calcium hydroxyapatite like crystals have been demonstrated in mitochondria of cardiac tissue which has undergone necrosis[39] Administration of labeled calcium chloride showed deposition of the calcium in mitochondria within the infarct if coronary occlusion was prolonged and followed by a period of reperfusion[40] Thus, accumulation of these crystals appears to be specific for infarction and is dependent on perfusion as well as necrosis The presence of calcium hydroxyapatite deposits in mitochondria from myocardial infarct zones similar to those found in bone suggests a possible mode by which bone seeking radionuclides accumulate in (and thus, identify) regions of acute infarction A donut like rim of increased radioactivity is seen frequently in experimental acute transmural infarctions and appears to correlate well with localization of calcium hydroxyapatite deposits in greatest concentrations[41] Of 19 dogs with acute coronary occlusion, all exhibited abnormal images at 24 to 48 hours after infarction A progressive decline in radioactivity was noted when injections were performed from two to 13 days after infarction Similarly, diminution in the calcium concentration in mitochondria from areas of infarction corresponded to the decreasing accumulation of ^{99m}Tc(Sn) pyrophosphate as a function of time after infarction Within two weeks after infarction, the major proportion of calcium deposits were replaced by granulation tissue This finding suggests a relationship between the binding of ^{99m}Tc(Sn) pyrophosphate and deposition of calcium deposits in mitochondria, however it is probably not the sole mechanism by which ^{99m}Tc(Sn) pyrophosphate accumulates in myocardial infarcts since the per cent of injected dose of ^{99m}Tc(Sn) pyrophosphate and ^{32}P labeled pyrophosphate was only ten to twentyfold greater in the mitochondria from infarct zones compared to normal areas However, a two hundred to six hundredfold increase in counts from homogenates of whole myocardial infarcts compared to homogenates of mitochondria from the infarct suggested that substantial deposition of the radionuclide occurs in subcellular loci other than mitochondria[42]

Since the pattern of accumulation of the tracer in transmural infarction corresponds to the location of densest migration of leukocytes to the periphery of the infarct an alternative mechanism might be that phagocytosis of the radionuclide is responsible for the production of an abnormal image However administration of cyclophosphamide to dogs with acute infarction did not preclude the production of positive images despite marked leukopenia Thus phagocytosis of ^{99m}Tc(Sn) pyrophosphate is an unlikely mechanism of accumulation[42]

The specificity of ^{99m}Tc(Sn) pyrophosphate for the detection of acute infarction has been studied by transient occlusion of the left coronary artery in dogs In this model, ischemia in the absence of infarction was not associated with a positive image[43]

In patients injection of ^{99m}Tc(Sn) pyrophosphate as early as 12 to 16 hours after infarction was associated with a positive image Optimal images are obtained one to three days post infarction but remain positive consistently for seven days and are usually normal after two weeks In one study of 23 patients the sensitivity

has nearly a thirtyfold greater ratio of activity in bone compared to infarct when compared to that observed with ^{99m}Tc polyphosphate Thus Fluorine is not likely to be a useful tracer because of problems of resolution related to its avidity for bone[6] Kinetic studies[63] of ^{99m}Tc polyphosphate and ^{18}Fluorine demonstrate that both radionuclides are cleared from the blood pool in a biexponential manner The first portion of the curve is thought to be due to rapid uptake by bone and the second portion is due to renal clearance ^{18}Fluorine clears faster from both portions of the curve since ^{99m}Tc compounds bind to red blood cells and plasma α 2 globulins (80 per cent of plasma radioactivity with ^{99m}Tc is protein bound compared to 15 per cent with ^{18}Fluorine Finally a comparison of the resolution and sensitivity of the images showed ^{99m}Tc polyphosphate to be a superior radionuclide[6]

Considerations for the future

Each of the radiopharmaceuticals mentioned have drawbacks The ideal infarct imaging tracer would have the following properties

1 High sensitivity and specificity for the diagnosis of acute infarction
2 Short half life permitting serial imaging
3 High infarct compared to normal tissue ratios of activity with little background activity
4 Early clearance from the blood pool
5 Early detection of acute infarction
6 Accurate estimation of infarct size
7 Non invasive administration (not requiring coronary injections)
8 Safety
9 Easy production of the tracer
10 Low cost

At present radiopharmaceuticals are being utilized primarily for the detection sizing and localization of acute myocardial infarction Perhaps a more detailed understanding of their mechanisms of accumulation will permit in depth study of the pathophysiology of the disease states and mechanisms of action of pharmacologic agents

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coronary artery bypass surgery,[5] there was a 16 per cent incidence of perioperative myocardial infarction judged by development of new Q waves and associated in each case with an abnormal ^{99m}Tc(Sn) pyrophosphate image This group included some patients with pre surgical or perioperative bundle branch block, and under scored the fact that not all new bundle branch blocks should be interpreted as resulting from a fresh infarction All patients with or without infarction exhibited elevated MB CPK activity Thus plasma enzyme elevations could not be used to detect infarction and ischemic injury in patients with operative trauma to the heart Since the electrocardiogram in this setting may also occasionally be equivocal, infarct imaging may be particularly useful as a specific index for the diagnosis of infarction

Potential clinical uses for ^{99m}Tc(Sn) pyrophos phate myocardial imaging include the diagnosis of (1) subendocardial infarction, (2) infarction in the presence of ventricular conduction distur bances, (3) recent infarction at a time when cardiac enzymes have returned to baseline, and (4) perioperative infarction (especially after coro nary artery bypass surgery)

Quantification of myocardial infarct size with radionuclides is being actively pursued experi mentally and clinically but results at present are inconclusive Good correlations have been ob tained when anterior wall infarcts in dogs were imaged with a gamma camera grid and computer interface 48 hours after infarction and images were compared with gross infarct weight at post mortem (r = 0 87) The best correlations were obtained with the left anterior oblique view grid computations *in vivo* and infarct weight (r = 0 92)[8] Planimetering infarct image area and correlating results with peak total CPK[57] in patients, or infarct weight estimated from morphology in dogs (r = 0 914) has been quite successful[58] Myocardial CPK depletion in experi mental infarction also correlates with tissue ^{99m}Tc(Sn) pyrophosphate activity (r = 0 89)[8]

Studies of patients have been less impressive however[54] use of ^{99m}Tc(Sn) pyrophosphate images in patients to categorize infarcts into large, medium or small groups failed to provide good correlations with peak total CPK or enzy matically estimated infarct size[43] Of 27 patients with myocardial infarction, ^{99m}Tc(Sn) pyrophos phate image areas correlated poorly with maxi mal precordial ST segment elevation (r = 0 39) or with the sum ST segment elevation (r = 0 47) In general infarct size is difficult to quantify in locations other than anterior Since the ratio of ^{99m}Tc(Sn) pyrophosphate activity in infarcts compared to normal myocardium was related to both the extent of necrosis and the degree of perfusion (as judged by injections of labeled microspheres in dogs with infarcts) merely measuring the number of counts in an area of infarct may not reflect infarct size alone[3] Hence, the markedly decreased flow to the necrotic center of an infarct is associated with only modest sequestration of ^{99m}Tc(Sn) pyrophosphate Also, problems related to overlap of bone resolution and sizing of three dimensional stuctures with a two dimensional system, all make infarct sizing less than optimal

Other bone scanning radiopharmaceuticals

^{99m}Tc(Sn) polyphosphate has similar physico chemical properties to those of ^{99m}Tc(Sn) pyro phosphate[60] ^{99m}Tc polyphosphate has been shown to accurately detect both transmural and subendocardial infarction in patients three to 20 days after infarction[61] As with ^{99m}Tc(Sn) pyro phosphate, correlations of scintigraphic localiza tion of infarction with electrocardiographic local ization is quite good Understanding some of the physico chemical properties of the tracer affords some insight into potential causes of false positive or false negative results Molecular weights of ^{99m}Tc polyphosphate between 4 000 and 6 000 daltons are optimal for imaging[60] Weights greater than 8,000 confer colloidal properties associated with localization of the tracer in the reticuloendo thelial system Weights less than 3 000 promote rapid renal clearance and little bone deposition Since ^{99m}Tc(Sn) polyphosphate (like other tech netium compounds) are made by reduction of ^{99m}Tc pertechnetate to ^{99m}Tc by $SnCl_2 \cdot 2H_2O$ ideal ratios of polyphosphate to tin have been established Ratios of 25 1 are optimal since less tin produces inefficient labeling and excess tin confers colloidal properties Also, the solid state of tin promotes greater complex stability since polyphosphate degrades at pH > 1 0[60]

A comparison of ^{99m}Tc polyphosphate with ^{99m}Tc(Sn) pyrophosphate in dogs with infarcts demonstrated ratios of radioactivity in infarcts compared to normal myocardium that were simi lar[62] ^{18}Fluorine another bone scanning agent

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suddenly changes from atrial fibrillation to a sinus rhythm Another tragedy from thromboembolism is the occasional occurrence of a devastating cerebral embolus in a patient who previously has had minimal symptoms from his mitral stenosis Other common secondary changes are the development of pulmonary hypertension and tricuspid insufficiency

The insidious slowly progressive nature of mitral valve disease invites continued medical therapy for the disease is primarily one of restriction of blood flow from the lungs so the left ventricle is not injured as occurs in mitral insufficiency or aortic valve disease Hence by restricting physical activity and using diuretics patients may be treated medically for decades with reasonably good results Ultimately however operation is usually required and also there is the ever present risk of thromboembolism Unfortunately when operation is done prosthetic replacement is often necessary and atrial fibrillation often remains permanent

Operative techniques

Open mitral commissurotomy at New York University has been routinely performed for several years using cardiopulmonary bypass using a standard technique with hemodilution a bubble oxygenator and roller pumps At a temperature of 25° C the aorta is intermittently clamped for 10 to 15 minutes intermittently unclamping the aorta with a large catheter vent in the root of the aorta to remove air after which the heart is defibrillated This combination of intermittent unclamping and periodically defibrillating the heart has proved a very reliable technique for resulting cardiac complications have been negligible

The tricuspid valve is routinely explored for insufficiency and when found corrected with a posterior leaflet annuloplasty in over 95 per cent of cases The only exception is when true organic tricuspid valve disease is present

The atrial appendage is carefully checked for thrombi, after which the orifice is routinely closed from within with a continuous suture of Prolene This is placed carefully with superficial bites to avoid injury to the adjacent circumflex coronary artery but has now been routinely done for over 4 to 5 years with only one instance of injury to the coronary artery occurring several years ago clearly from a technical error It is surprising that the technique of routine closure of the atrial appendage has not been widely adopted because of the well known problem of continued fibrillation in patients who have been fibrillating for a long time before operation is performed In patients with a prosthetic valve replacement who remain in atrial fibrillation it of course is impossible to tell whether a subsequent episode of thromboembolism originated from the prosthetic valve or the fibrillating appendage

Commissurotomy is performed by incising the fused commissures throughout their length stopping a short distance from the annulus usually only a few millimeters where the commissure ends The commissurotomy is never carried completely to the annulus because a true commissure does not extend to the annulus as small accessory leaflets are present The change from a thickened fused commissure to a thin area is a clear technical guide to indicate where the commissurotomy should be stopped

In some patients commissurotomy is extremely simple while in others it is complex and difficult Several techniques of exposure are crucial including cardiac arrest a wide atrial incision and proper positioning of a malleable retractor to expose the mitral valve Shifting the retractor as little as 2 cm can greatly impair visualization

The key guide in commissurotomy is being certain that the mobilized leaflets are attached to the underlying chordae In some instances the chordae actually lie close to the under surface of the fused commissure and can be readily severed if the anatomy is not clearly visualized The triple right angle technique emphasized by Mullin and associates[3] in 1974 has been routinely used and remains very valuable

A more difficult technical problem which well illustrates the advantage of open over closed commissurotomy is found when chordae are fused and often shortened to approximate the fused commissure to the underlying papillary muscle By carefully separating the commissure the underlying papillary muscle can be split and also the fused chordae separated obtaining a functional valve that would normally be replaced and certainly could not be adequately opened with a closed digital commissurotomy

A technique that has greatly facilitated radical commissurotomy is the ability to detect mitral insufficiency at the time of operation and correct this with sutures or an annuloplasty if necessary

A plea for early, open mitral commissurotomy

Frank C Spencer M D
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The concept developed in this short report is that technical advances with open mitral commissurotomy have progressed to where operation should be considered at a much earlier stage than is usually done at present Specifically, available data[1-5] support the concept that open mitral commissurotomy should be almost routinely performed in a patient with few symptoms a small gradient at catheterization and a calculated cross sectional valve area decrease to 1 3 to 1 5 square centimeters It is similar to the recommendation of operation for a healthy asymptomatic 16 year old child with a large atrial septal defect and a pulmonary blood flow three times normal Even though the child can usually function well for years without operation the long term course is well known, so early operation is routinely advised

A major concept underlying the importance of early operation is that a radical valvulotomy, not only eliminating the gradient but opening the valve as much as possible without producing insufficiency, may *prevent* progressive fibrosis from turbulent flow of blood which in turn will require prosthetic replacement rather than reconstruction when operation becomes necessary months or years later

Etiologic considerations

Two different pathologic processes are probably significant with rheumatic mitral valve disease Virtually everyone agrees that the basic cause is rheumatic fever What is not readily recognized is the concept proposed by Selzer and Cohn[6] that the continuing turbulent flow of blood, produced by the orifice malformed by the rheumatic inflammatory process, leads to progressive fibrosis thickening and calcification at an unpredictable rate This may occur within a few years or may extend over three or four decades It is not unusual for a patient in the sixth decade with a distinct rheumatic history in the late 'teens' or early twenties" to remain minimally symptomatic for the next 20 to 30 years but eventually progress to severe calcific mitral stenosis requiring prosthetic replacement The process is similar to that now well recognized in congenital aortic stenosis with a biscupid valve where patients may not develop calcific aortic stenosis until the sixth or seventh decade of life Hopefully, early radical commissurotomy that decreases the turbulent flow of blood may prevent these late changes

Pathologic processes

Three basic processes occur with mitral valve disease The simplest and most common is fusion of the commissures from the rheumatic inflammation A more advanced injury is fusion and shortening of the underlying chordae often depressing the fused commissures down to the underlying papillary muscle The third most severe injury is thickening and subsequent calcification of the valve leaflets which could result from the mitral inflammatory process but probably more commonly results from long standing turbulent flow like that with aortic valvular disease When this occurs repair is virtually impossible

Serious secondary changes are the inevitable development of left atrial hypertrophy soon followed by atrial fibrillation and the ever present risk of thromboembolism from thrombi accumulating in the fibrillating appendage On a few occasions the author has found 3 to 4 mm thrombi at operation lying *freely* in the atrial appendage like peas in a pod This may be the mechanism of acute embolism in the patient who

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Increase of WBC CRP, and BSR following cardiac pacemaker implant

The author has noted transient increase of serum C reactive protein (CRP) white blood corpuscles (WBC) and blood sedimentation rate (BSR) following pacemaker implant In 25 consecutive patients WBC CRP and BSR were frequently checked following cardiac pacemaker implant The average age of these 25 patients was 53 8 years. Pacemaker units employed in this series were all CPI Maxilith (models 401 and 301) All 25 cases that had received endocardial pacing showed an uneventful postoperative course without any fever or infection Examinations of WBC CRP and BSR were done preoperatively on the first postoperative day (the day after surgery) and on the second the third the fifth, and the seventh postoperative days

WBC showed a wide variety among cases Preoperative WBC was expressed as 100 in each case and postoperative WBC was shown by means of an index number compared to the preoperative number The marked increase of WBC was noted on the first postoperative day in all cases. The highest index was 227 the lowest 107 The average index was 155 ± 30 (± 30 was the standard deviation) on the first day It was 146 ± ?4 on the second day and 122 ± ?? on the third day The index returned to th preoperative level on the fifth day showing 104 ± 17 It was 96 ± 9 on the seventh day when some cases showed less than preoperative indices

CRP was classified into the following groups in our labora tory – +– 1+ 2+ 3+ 4+ 5+ and 6+ Both – and +– were included in – (negative) group In order to calculate average value of CRP – (negative) was expressed as "zero" CRP The average was 1 9+ on the first 3 4+ on the second 3 1+ on the third 1 7+ on the fifth and 0 8+ on the seventh postoperative days The highest rise was noted on the second day On the seventh day 2? out of 25 cases got to negative or 1+

BSR was measured by the Westergren method Only the rate of the 60 minute interval was compared Preoperative BSR was 11 ± 6 mm (±6 was the standard deviation) on the average On the first day it was 16 + 10 mm It was 28 ± 12 mm on the second day 3? ± 17 mm on the third, 36 ± 19 mm on the fifth day and 33 ± 18 mm on the seventh BSR showed a gradual increase following implant reaching its maximum level on about the fifth postoperative day and being normalized in three weeks.

WBC is increased and decreased more promptly than CRP The latter precedes the rise in BSR. The schema of these three parameters was drawn in Fig 1 WBC shows the fastest CRP the middle and BSR the slowest changes Physicians have to remember these usual changes of WBC CRP and BSR following pacemaker implant in order to differentiate these changes from any acute infection acute myocardial infarc tion rheumatic fever tuberculosis etc

As various artificial organs are increasingly implanted in the human body more attention should be paid as to changes in these parameters.

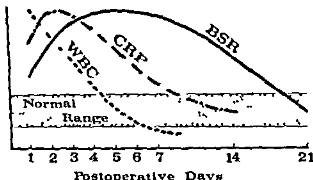


Fig 1 Diagrammatic representation of WBC CRP and BSR showing postoperative rise and fall following pacemaker implantation See text for explanation

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Significance of nausea and vomiting during acute myocardial infarction*

Early diagnosis of myocardial infarction is crucial but often difficult Diagnostic importance of extracardiac manifesta tions has been emphasized in the past In patients with acute myocardial infarction the symptom complex of nausea and vomiting has previously been referred to as non specific or as a result of analgesic therapy →

This study was undertaken prospectively to evaluate the diagnostic and prognostic significance of nausea and vomiting in patients with acute myocardial infarction

Supplemented by Grant (GR 2 ES 75) from Essex County Heart Association, affiliate of the American Heart Association

This is done by retrograde insertion of a catheter with multiple perforations across the aortic valve, as described by Mullin and colleagues

Rarely debridement of calcium may be feasible for annuloplasty may be combined with commis surotomy [3]

Clearly techniques of mitral reconstruction *rather than replacement* are still evolving, evidenced by the work of Carpentier in Paris [4] Reed [3] at New York University and Rumel [5] in *Salt Lake City* An important concept is that reconstruction is probably far more feasible and durable than has been considered possible in the past

This aggressive, radical commissurotomy has now been performed at New York University for several years The technique has a very low mortality rate in the range of 1 to 3 per cent Recurrent stenosis has not been seen in any patient operated on by the author in the last ten years and the only late complication observed has been the development of insufficiency in patients in whom fibrosis and distortion of the leaflets were already present undoubtedly the result of continued turbulent flow of blood and fibrotic contraction Recurrent emboli have also been virtually unknown since the policy of routinely closing the atrial appendage was adopted several years ago

It is *well recognized* that this concept may never be proved statistically because of the long progressive course of mitral valve disease often extending over three to five decades, and also because the relative frequency of reconstruction versus replacement will vary not only with the experience and attitude of the surgeon but with the type of valve pathology seen by him For example, a surgeon experienced and enthusiastic about reconstruction might perform commissurotomy in 95 per cent of cases if patients are referred for operation with relatively early disease while a similar surgeon might find it necessary to perform replacement in over 30 per cent of cases if patients are referred only with far advanced disease and extensive calcification

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tors emphasized the precipitability of nephritogenic antibody observing that immunologically responsive rabbits developed chronic glomerulitis provided only that the daily antigen injection was sufficient to remove circulating antibody and maintain temporary antigen excess. Similarly in SLE the human analogue of chronic serum sickness controversy exists concerning the role of antibody precipitability in the pathogenesis of renal disease Using the technique of counterimmunoelectrophoresis to examine SLE sera a high degree of correlation was demonstrated between renal involvement and the absence of precipitating DNA antibody with 64 to 75 per cent of patients with lupus nephritis having no demonstrable precipitins. The measurement of spontaneously precipitating and total DNA antibody by radioimmunoassay however has led to the conflicting observation that all lupus patients with clinically determined mild or severe nephritis had precipitating DNA antibody

We sought to clarify this issue by designing a study which differed from previous investigations in the following ways (1) All patients with nephritis were biopsied and the tissue obtained thoroughly characterized by light immunofluorescent and electron microscopy ( ) the biopsy and serum specimens from all patients were obtained prior to instituting corticosteroids or immunosuppressants thereby removing therapy induced alterations of antibody quantity or character and (3) precipitating antibody from the test serum was measured both by radioimmunoassay and counter immunoelectrophoresis Our results (summarized in Table I) demonstrated that patients with diffuse proliferative nephritis or active lupus without renal involvement evidenced a vigorous native DNA antibody response with a significant amount being precipitating in character In contrast patients with membranous nephropathy were unique in synthesizing significantly less total native DNA antibody essentially all of which was non precipitating

If non precipitating antibodies to DNA are less efficient at complement fixation and possibly immune elimination of antigen membranous lupus nephropathy may be a consequence of the persistence in the circulation of complexes of DNA with non precipitating antibody and the infiltration of the glomerular capillary wall (GBM) with such complexes leading to membranous thickening without significant inflammation Alternatively since free DNA is frequently demonstrable in the circulation of SLE patients and the GBM has a high affinity for such DNA membranous lupus nephropathy may result from local formation at the GBM of complexes involving DNA and non precipitating DNA antibody In summary the formation of complexes with native DNA and non precipitating DNA antibody either in the circulation or in situ may well be essential to the development of membranous lupus nephropathy

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Table I Summary of native DNA antibody profiles of patients with diffuse proliferative nephritis (PRO) active lupus without renal disease (NO) and membranous nephropathy (MEM)

	PRO	NO	MEM
Mean total DNA antibody (%)	96.2	69 9	26 6
Mean precipitating DNA antibody (%)	62 9	52.4	< 1
Ratio†	0 66	0 66	0 04
Range of total DNA binding capacities (ng/ml)	> 2 537 26 624	> 2,355-13 107	49 627
Number of patients positive in counter immunoelectrophoresis‡	4/4	4/4	1/5

Radioimmunoassay results expressed as precentage of [14]C DNA bound by antibody
†Ratio = precipitating/total DNA antibody
‡Precipitin reaction of test serum with 20 5 or 1.25 mg DNA/mL

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Table I Patients with acute infarction

	All	Anterior	Inferior
1 Number	62	33	29
2 Males	47	28	19
3 Females	15	5	10
4 Age (years)	60 1 ± 1 5	61 2 ± 2 1	59 ± 2.3
5 Nausea/vomiting	29	9	20*
6 Bradyarrhythmia	18	4	14

P vs anterior wall infarct < 0 01 0 001

Sixty two patients with a diagnosis of acute myocardial infarction admitted to the Coronary Care Unit of St Joseph s Hospital in Paterson New Jersey were interviewed for the presence of nausea and/or vomiting by one of the authors before the administration of analgesics None had previous gastrointestinal disorders diabetes hypertension or cerebral dysfunction or a heavy meal preceding the present episode Subsequent follow up *was carried out during the hospitaliza*tion period especially with regard to continuous nausea or vomiting drugs administered arrhythmias and enzyme changes

Of the 62 patients 33 (53 per cent) had anterior and 29 (47 *per cent) had inferior wall myocardial infarction The diag*nosis of acute myocardial infarction was confirmed by charac teristic chest pain serial electrocardiographic and cardiac enzyme changes

While only nine out of 33 (27 per cent) patients with *anterior wall myocardial infarction complained of nausea and* vomiting this symptom was present in 20 of 29 (69 per cent) *patients with inferior wall myocardial infarction* (chi square = 9 2 P < 0 003) (Table I)

Nausea and vomiting in inferior wall but not anterior wall myocardial *infarction was associated with bradyarrhythmias* (P < 0 05) In contrast patients complaining of nausea and vomiting with anterior wall but not with inferior wall were younger (53 ± 1 vs 64 ± 2 years) and had higher enzyme values on admission (SGOT 449 ± 56 vs 289 ± 34 LDH *815 ± 87 vs 357 ± 69) (all Ps < 0 05) The higher enzymes in* this group probably reflected heart failure which was present in all nine cases of AMI with nausea and vomiting (P < 0 05) and CPK values were similar

The *four subgroups differed* insignificantly with regard to pain characteristic blood pressure tachyarrhythmias and *hospital stay*

These data indicate that the nausea and vomiting are an important symptom complex in the diagnosis of myocardial infarction These symptoms could be used as guides in the anatomic location of infarct as they are more frequently associated with inferior *wall than with anterior wall myocar*dial infarction (69 vs 27 per cent)

Cardiogenic vomiting has been attributed to *cardiogenic* shock because of association of sweating and pallor In the present study in anterior wall myocardial one of the patients *who had nausea and vomiting* had cardiogenic shock Conversely of the three patients with anterior wall myocar dial infarction who developed cardiogenic shock none had nausea or vomiting

Thus the mechanism of this symptom complex appears to *be based* on the vaso vagal reflex This is borne out by the fact that the bradycardia which results from the reflex vagal activity like nausea and vomiting *is more frequently noted in* patients with inferior than with anterior wall myocardial infarction

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A unique antibody response associated with *the development of membranous nephropathy* in systemic lupus erythematosus

The importance of qualitatively different populations of antibody in determining the inflammatory potential of circu lating immune *complexes in animal models of chronic serum* sickness and human *systemic lupus erythematosus* (SLE) is well known The precise role of antibody precipitability however is unclear since numerous investigations have yielded seemingly conflicting results

In rabbits chronically immunized with *bovine serum* albu min one group of investigators noted that in contrast to the rapidly eliminated immune complexes *formed by animals* without nephritis rabbits with nephritis formed significant amounts of non precipitating antibody The lesser avidity for the reticulo-endothelial system of the small complexes formed by non precipitating antibody was *thought to lead to slower clearance and nephrotoxicity In the same* animal model of chronic serum sickness however another group of investiga

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tors emphasized the precipitability of nephritogenic antibody observing that immunologically responsive rabbits developed chronic glomerulitis provided only that the daily antigen injection was sufficient to remove circulating antibody and maintain temporary antigen excess Similarly in SLE the human analogue of chronic serum sickness controversy exists concerning the role of antibody precipitability in the patho genesis of renal disease Using the technique of counterimmu noelectrophoresis to examine SLE sera a high degree of correlation was demonstrated between renal involvement and the absence of precipitating DNA antibody with 64 to 75 per cent of patients with lupus nephritis having no demonstrable precipitins. The measurement of spontaneously precipi tatin and total DNA antibody by radioimmunoassay however has led to the conflicting observation that all lupus patients with clinically determined mild or severe nephritis had precipitating DNA antibody

We sought to clarify this issue by designing a study which differed from previous investigations in the following ways (1) All patients with nephritis were biopsied and the tissue obtained thoroughly characterized by light immunofluores cent and electron microscopy (?) the biopsy and serum specimens from all patients were obtained prior to instituting corticosteroids or immunosuppressants thereby removing therapy induced alterations of antibody quantity or charac ter and (3) precipitating antibody from the test serum was measured both by radioimmunoassay and counter immuno electrophoresis. Our results (summarized in Table I) demon strated that patients with diffuse proliferative nephritis or active lupus without renal involvement evidenced a vigorous native DNA antibody response with a significant amount being precipitating in character In contrast patients with membranous nephropathy were unique in synthesizing signif icantly less total native DNA antibody essentially all of which was non precipitating

If non precipitating antibodies to DNA are less efficient at complement fixation and possibly immune elimination of antigen membranous lupus nephropathy may be a consequence of the persistence in the circulation of complexes of DNA with non precipitating antibody and the infiltration of the glomerular capillary wall (GBM) with such complexes leading to membranous thickening without significant inflam mation Alternatively sinc free DNA is frequently demon strable in the circulation of SLE patients and the GBM has a high affinity for such DNA membranous lupus nephropathy may result from local formation at the GBM of complexes involving DNA and non precipitating DNA anti body In summary the formation of complexes with native DNA and non precipitating DNA antibody either in the circulation or in situ may well be essential to the development of membranous lupus nephropathy

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Of the sham operation

Because of the tremendous number of coronary artery bypass operations performed each day and the astronomical costs even by present standards and the good results reported even when the shunts are closed[1] there is a great need for evaluation of this operation by sham bypass surgery (operations in which the heart is exposed and the pericardium opened but no actual shunts done) as well as evaluation of the effects of the mere existence of surgery All sham operations must be performed as a double blind therapeutic test procedure Before a drug a medical type of therapeutic agent is approved by the FDA for general use, even for less serious and less hazardous illnesses the agent must be evaluated by double blind or sham studies Why are there not the same strict standards of testing for a surgical therapeutic agent? There is a definite need for sham coronary bypass operations to evaluate coronary bypass surgery Of course there is an ethical problem to be considered

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Menstruation and heart disease

To The Editor:

I was intrigued by Seely's editorial (March 1976 issue)[1] which suggests that menstruation may play a role in protecting women against heart disease—surely one of the few beneficial things that have been written about menstruation in the course of medical history and appropriate to current feminist concepts. He then alludes to a possible beneficial role of venesection, that mainstay of medieval medicine.

One of the ways to check this theory would be to look at cardiovascular mortality rates in blood donors, and I would be interested to know if anyone has any information on this. Demonstration of a beneficial effect of blood donation would be a welcome aid to sorely pressed blood banks around the world.

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Blood donors and coronary disease

To the Editor:

In reply to Dr. Goodyear's letter, may I say, first of all, that the appropriateness of my views to current feminist concepts as well as their possible resemblance of medieval practices are purely accidental.

I have not realized that I made medical history by being the first to say a kind word about menstruation. I certainly do not know of anyone having done so in the past, but Shakespeare might have had the same idea when pointing out that every cloud had a silver lining. He did not make his meaning entirely clear, but then he used only six words as against 3,000 in my article.

As far as I know, no literature is available on differences in cardiovascular mortality rates between blood donors and a suitable control group. Before I called attention to the possibility that it could be hemorrhages, not estrogens, that may have a prophylactic effect on atherogenesis, it does not seem to have occurred to anyone to carry out such a survey. After the publication of the article the possibility seems to have generated some interest. Investigation concerning mortality rates of blood donors, particularly *male* blood donors, has already been suggested twice to me in correspondence related to the article, notably by Dr. B. Moors, the University of Manchester, and by a doctor in Hospital Cantonal Geneve, whose name I could not decipher. I cannot carry out such an investigation myself, but I would be glad if someone did. There are two alternatives such a survey could take. It would be possible to select a group of male blood donors, preferably in the over forty age groups, whose future medical history would be followed. Alternatively it would be possible to select a group who were blood donors, let us say, 20 years ago and attempt to trace their history in the intervening years. Obviously, the disadvantage of the first method is the long time it would take to obtain statistically significant results, and of the second the great difficulties and expense involved in tracing the fate of the selected groups.

A considerable amount of research has been done on the allied subject of differential resistivity of women with early and late onset of menopause, the early onset being due either to natural causes or ovariectomy. A recent leading article in the *British Medical Journal*[1] gave a somewhat sketchy survey of the past literature dealing with the subject, as well as some editorial opinions, the latter hotly debated in subsequent editorial correspondence.[2,3] The most interesting of the quoted references is a Swedish study[4] comparing the menstrual histories of women with known coronary heart disease with a randomly selected control group. According to this, 76 per cent of the women admitted to hospital with myocardial infarction had passed through the menopause before the age of 50, in comparison with 48 per cent of the controls. In women, however, the cessation of menstrual hemorrhages is inseparable from hormonal changes, so that it is impossible to know with certainty which one of these factors affects resistivity to coronary heart disease. This is the reason why an investigation on male blood donors would be important.

I might perhaps add that I wrote two subsequent papers to the article under consideration. One is published in the November 1977 issue of *Medical Hypotheses*,[5] the other on "The atherogenic effect of stilbestrol" was recently submitted to AMERICAN HEART JOURNAL.

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Overdiagnosis of left anterior hemiblock

To the Editor:

In the October 1977 issue of THIS JOURNAL Dr. G. E. Burch cautions against overdiagnosing left anterior hemiblock (LAH). This caution is *justified*, but Rosenbaum, in his

monograph discussed the differences between this form of fascicular block and horizontal heart with clockwise rotation LVH etc His criteria included an axis of –60 degrees–but at least –45 degrees In Dr Burch s example the axis is not that far to the left Other possibilities of incorrectly diagnosing LAH include inferior infarction with large Q waves aberrant conduction due to pre excitation and others In the case of LVH the question still has to be solved if an axis of –60 degrees in LVH could not be due to fascicular block caused perhaps by stretching of the septal fibers

Of course the diagnosis of LAH per se does not imply a grave prognosis and in an asymptomatic patient a pacemaker is certainly not indicated

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Retrograde Wenckebach phenomenon in ventricular tachycardia

To the Editor

The purpose of this letter is to present a rather rare ventriculoatrial conduction during ventricular tachycardia documented by intracavitary (IC) recordings

In a 69 year old man with resistant ventricular tachycardia antiarrhythmic drugs and four electric shocks had been without result Therefore a tripolar electrode catheter was inserted into the right heart and short periods of ventricular overdriving succeeded in converting the heart to sinus rhythm

The IC electrograms recorded during arrhythmia from the right atrium show a retrograde ventriculoatrial conduction with a progressive prolongation of the ventriculoatrial interval followed by a nonconducted ventricular beat thus a retrograde Wenckebach phenomenon as shown on the two IC electrograms recorded simultaneously [1]

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Fig 1 A simultaneous recording of three intracavitary electrograms from the right atrium *(ICRA)* In the bottom panel is a diagrammatic presentation Paper speed 50 mm per second *A* = Atrial activity *V* = ventricular activity

Book reviews

Coronary Artery Surgery A Critical Review By Thomas A Preston M D New York 1977 Raven Press 270 pages Price $12 50

The title of this book summarizes very well its contents. The author has reviewed papers published supporting and attacking bypass surgery for coronary artery disease This of course is interesting to the readers of this book but those who have followed the literature closely and without bias know that this approach will not decide the value of coronary artery bypass surgery As the author states in conclusion on page 257 coronary artery surgery is neither proven nor disproven as a beneficial mode of therapy And Dr Preston is correct but what justifies this book? Readers who have not followed the literature closely or who have only read or accepted one point of view will find both the pro and con points of view reviewed The historical chapter should interest young surgeons and cardiologists who did not know Claude Beck, or do not know Vineberg and others who pioneered the surgical management of coronary artery disease The chapters on placebo effects, psychological factors and financial incentives deal with well known factors in therapeutics to clinicians and need discussion

It is interesting that Preston writes about courageous editorialists who indicated the need to evaluate operations This requires no courage it is only an obvious demand for reliable and objective data indicating definite value for any therapeutic agent before it is employed or recommnded to less informed physicians There certainly is a need to know what is right."

In summary this is an interesting book but the reader will find no answer as to the value of bypass surgery nor unfortunately even a recommendation to withhold surgical therapy until a definite answer as to its value is obtained This would suggest that Preston is of the opinion that bypass surgery is an acceptable procedure even without proof of its value whereas the criteria of the FDA requires established therapeutic value of medicinal agents prior to recommendation of their general use in medicine In fact the FDA disapproved Laetril since its effectiveness has not been established or proven Why use different standards or different criteria for coronary bypass surgery?

Therefore after an extensive review of the literature this book does not answer the question Is coronary bypass surgery useful for ischemic heart disease and if this is not known, should it continue to be performed at the present tremendous rate? And, what should doctors advise their patients to do at present? Undergo an expensive operation of unproven therapeutic value?

Physiology of the Heart and Circulation By Robert C Little Chicago 1977 Year Book Medical Publishers Inc 334 pages.

This paperback book on physiology of the heart and circulation contains an excellent brief review of the physiology of cardiac and circulatory function The author has presented principles which are generally accepted The relationship of function to structure and disease is clearly and briefly presented. The 14 chapters include discussions of fluid movement cardiac structure electrophysiology and electrocardiography cardiac dynamics cardiac work hemodynamic phenomena structure of the blood vessels and venous and pulmonary circulations. The illustrations are well chosen and the bibliography carefully selected This book should interest all physicians who treat diseases of the heart and circulation as well as medical students It should be included among books recommended to medical students and housestaff

Nuclear Cardiology Principles and Methods Edited by Aldo N Serafini Albert J Gilson and William M Smoak, New York and London 1977 Plenum Medical Book Company 249 pages. Price $22 50

Nuclear medicine is a rapidly expanding field in medicine The application to clinical cardiovascular states is likewise *increasing rapidly However like all developing methods and* their applications the interpretation of data offers difficulties. The physician must learn to know when the method is useful in his practice With critical review of this book readers will find the use of nucleides to have limited supplemental value in the practice of cardiology For example is it to the patient's best interest during the early phases of a fresh infarct of the myocardium to be transferred to a nuclear medicine laboratory to attempt to delineate the area of infarction when it can be done at the bedside with a properly recorded electrocardiogram? And what about the cost? Regardless of these and other aspects of the problems related to nuclear cardiology the cardiologist at least must be well informed of presently active interests in cardiology This book describes the field very well The book is divided into five parts to which others knowledgeable in nuclear cardiology contribute The five parts are concerned with fundamental principles, shunt detection in congenital heart disease evaluation of myocardial blood flow evaluation of ventricular function and the role of radioimmunoassay in cardiology These subjects are reviewed very well and from the viewpoint of clinical cardiology rather than laboratory research. Those involved in nuclear cardiology as well as the practicing physician will find the book useful This reviewer hopes that readers will not consider this type of study superior to others nor assume that the methods are fully evaluated and developed Nevertheless this is a timely book which includes aspects of an important subject into a single volume for the convenience of many cardiologists and internists.

Advances in Cardiology volume 20 Future Directions in the Management of Cardiac Disease Edited by John H K Vogel, New York 1977 S Karger AG 143 pages

This publication summarizes the Seventh Conference on Cardiovascular Diseases held in Aspen Colorado during January 19 6 The eleven papers included in this book review primarily coronary artery disease and left ventricular function Prevention and maintenance of good cardiac health are the main points of emphasis Bypass surgery and medical care for ischemic heart disease constitute a prominent part of the discussions The reader will find this to be a mature review of important problems in cardiology The discussions of prevention of coronary heart diseases, coronary artery dysfunction " integrated medical-surgical treatment of pre infarction syndrome and the results of repair of congenital heart defects are among the subjects discussed This volume of *Advances in Cardiology* is another good one and certainly worth owning

Books received

Disorders of Hemostasis in Surgery Edited by Witold J Rudowski Hanover New Hampshire 1977 The University Press of New England 456 pages Price $17 50

Infective Endocarditis Edited by Edward L Kaplan M D and Angelo V Taranta M D Dallas 1977 American Heart Association 86 pages Price $6 00

Medical and Health Information Directory Edited by *Anthony T Kruzas Detroit 1977* Gale Research Company 664 pages Price $48 00

Intensive Coronary Care A Manual for Nurses *third edition* By Lawrence E Meltzer M D Rose Pinneo R N and J Roderick Kitchell Bowie Maryland 1977 The Charles Press Publishers 274 pages Price $20 88

Exercise in Cardiovascular Health and Disease Edited by Ezra A Amsterdam M D Jack H Wilmore Ph D and Anthony N DeMaria M D New York 1977 Yorke Medical Books 376 pages Price $33 00

Announcements

Medex 78

Medex 78 the Fourth International Exhibition for Medical Electronics and Bioengineering will take place in the halls of the Swiss Industries Fair in Basle Switzerland from June 6 to 10 1978 In conjunction with the exhibition a technical *meeting on computer tomography (CAT) will be held on June* 6 and 7 under the chairmanship of Professor M Anliker and Dr P Ruegsegger from the Institute of Biomedical Technology of the Federal Institute of Technology and the University of Zurich

For further information regarding the exhibition and meeting please contact The Secretariat Medex 78 c/o Swiss Industries Fair P O Box CH 4021 Basle Switzerland Telephone 061/26 20 20 Telex collect 62685

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Fifth European Congress of Anaesthesiology

The Fifth European Congress of Anaesthesiology will be held in Paris on September 4 through 9 1978 There will be 70 sessions in seven lecture halls Simultaneous translations will be provided *in English French German and Spanish Topics* covered will be hemodynamic variations in anesthesia in obstetric anesthesia and analgesia anesthesia for vascular surgery pediatric anesthesia anesthesia for emergency surgery anesthesia for cardiac surgery and sodium nitroprusside in clinical practice—anesthesia and resuscitation Also presented will be anesthesia and resuscitation problems in neurosurgery emergency surgery traumatologic surgery radiology E N T surgery ophthalmological surgery digestive surgery urological surgery surgery in the aged thoracic surgery gynecological and obstetrical surgery orthopedic surgery problems due to intoxication and pharmacology and clinical use of new muscle relaxants

For registration information and registration requests for free papers and films please contact Congres Anesthesie—P M V B P 246 92205 Neuilly sur Seine France

Society of Nuclear Medicine meeting

The Third Annual Western Regional Meeting of the Society of Nuclear Medicine will be held at the Hotel Vancouver in Vancouver *B C* Canada *on October 13 14 15 1978 The* Northern California Southern California Pacific Northwest and Hawaii Chapters are sponsoring this meeting *The* program will consist of invited papers contributed papers *registry review courses for technologists* and refresher courses for physicians The Scientific Program Committee welcomes the submission of abstracts of original *contributions in* nuclear medicine for the Third Annual Western Regional Meeting Physicians Scientists and Technologists *members and nonmembers* are invited to participate The Program will be structured to permit the presentation of papers *from all* areas of interest in the specialty of Nuclear Medicine Abstracts submitted by technologists are encouraged and will be presented at the scientific program Abstracts for the *scientific program will be printed in the program booklet* and will be available to all registrants at the meeting

Please address all correspondence regarding the submission of abstracts and the exhibiting of commercial companies to Justine J Lynch *Administrative Coordinator* P O Box *40279 San Francisco CA 94140 Telephone* (415) 647-0722 or *647 5909*

American Heart Journal

June 1978 Volume 95 Number 6

Editorial

Inferior vena caval interruption in the prevention of fatal pulmonary embolism

A M N Gardner DM MCh FRCS
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When medical measures to control pulmonary embolism fail or are contraindicated mechanistic approaches can save lives

The surgery entailed is sufficiently safe for prophylactic application in certain cases for example when mandatory operations have to be performed on patients with thromboembolic disease particularly when anticoagulant therapy is contraindicated

Trousseau was the first to suggest the interposition of a barrier between the thrombus and the large veins in cases of pulmonary embolism This was in *1868* twelve years after Virchow s first account of the pathological features of the condition Only now a century later is it possible to evaluate the various physical methods of preventing fatal pulmonary embolism

Pathological and hemodynamic considerations

The clinicians picture of pulmonary embolism shows only the tip of the iceberg since small clinically undetectable emboli are the rule rather than the exception in ill and elderly patients [3,5] Indeed it might be better for them to speculate on which patients have not had emboli rather than the reverse Small emboli are usually (satisfactorily) lysed in the lungs but some remain as the strands and bands described by Virchow (1860) in the pulmonary arteries Such strands may arise from the lysis resistant platelet elements (Zahn s lines) in the thrombus They are also commonly seen in the long veins after thrombosis where they may arrest small emboli arising more peripherally and so cause recurrent local thromboses It takes a large pulmonary embolus to produce symptoms and only emboli of 7 5 mm or more in diameter' are likely to be lethal although the size of the patient and any degree of pre existing blockage to the pulmonary arterial tree are relevant

Most lethal emboli arise from the leg or pelvic veins but emboli from the subclavian veins particularly after parenteral feeding can be *fatal* Two such cases were recognized only at autopsy when it was realized that the emboli in the lungs were too large to have traversed the site of the partial vena caval occlusion Judging from the literature right atrial and hepatic vein origins of emboli are much less common

In patients suffering from thromboembolism peripheral thromboses are usually multiple and their propagation is often extremely rapid being *measured in hours* rather than in days This process may be exacerbated by peripheral phlebography For these reasons the concept of total *phlebography* of legs and pelvis followed by appropriate local surgery to lock in the clot [8] is unsound furthermore this technique seldom adequately demonstrates the internal iliac veins which are the source of about 10 per cent of fatal emboli

The inferior vena cava is the final common path of the great majority of dangerous emboli and is thus the optimal area for their surgical arrest Local narrowing by surgery to prevent the

From the T rb y Hosp tal, T rqu y Engla d
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Reprint eq ests Dr A. M N G rdner Torb y Hosp tal T qu y Devo TQ 7AA Engl d

onward passage of dangerous sized emboli has obvious advantages over complete ligation though of course the subsequent arrest of any large embolus will make the partial occlusion complete Caval recanalization is the exception rather than the rule and is usually incomplete

Criteria therefore for a satisfactory method of partial caval occlusion are first that it should reliably arrest emboli of a lethal size (7 5 mm) in diameter, secondly that it should not tend to become blocked by the unnecessary arrest of common insignificant small emboli, and thirdly that the narrowed area should have the largest possible cross section to allow free flow of blood

Fig 1 illustrates the various methods of partial caval occlusion Intraluminal filters and plications have the disadvantage that they arrest saddle fashion the common small clinically insignificant emboli, and moreover they soon distort and allow the passage of lethal sized emboli Foreign material such as filters introduced into the lumen of the inferior vena cava become covered with a pseudo neointima that may proliferate greatly like vegetations on a heart valve A comparative study of plications, filters and smooth external clips performed in a series of patients with inoperable abdominal neoplasms and so at a special risk from thromboembolism, showed clearly that the clips were superior Not only were they highly effective, but they more commonly remained patent than other methods of partial occlusion [3]

External clips of various designs have been used to narrow the lumen of the cava unlike intraluminal devices their application does not encourage primary thrombosis [3,9] Serrated clips[10,11] have been popular, but they produce multiple discrete channels that have a smaller total cross sectional area of lumen than that of smooth clips They are also likely to arrest small emboli saddle wise on the pillars' between the channels, these considerations together with the extra difficulty and potential danger of application suggest that they should be superseded by smooth clips whose safety and effectiveness is now well established

The ideal smooth clip should be designed for oblique placement low on the cava to give maximal cross sectional area to the narrowed part *

Such clips are obtainable from F J Payne and Son Mill Lane Osney Oxford

In people of average build a 5 5 mm gap has proved effective In large men the gap has been widened to 6 0 mm and in small women it has been narrowed to 5 0 mm and in one case of paradoxical embolism with normal pulmonary pressures, a 4 0 mm gap was used in such cases caval ligation might be wiser if pulmonary pressure is raised The wall of the vena cava is 0 5 mm thick so in all cases the true lumen is 1 0 mm smaller than the gap in the clip

Partial caval ligation with or without beads[12,13] is simple (see Fig 1), but produces an undesirably small lumen Complete vena caval ligation is mandatory in cases of septic embolism, in cases where dangerous embolism continues after partial occlusion, and when pulmonary hypertension increases after such an operation Ligation in ill patients particularly those with cardiovascular disorders, carries a high mortality rate (10 to 50 per cent) from fluid sequestration in legs and pelvis The efficiency of the collateral venous circulation varies considerably from patient to patient, it is most efficient in women with intact ovarian veins, most of whom develop only minor transient leg swelling after lower caval ligation The optimal site for both partial and complete caval occlusion is as low as possible in the inferior vena cava The collateral circulation here is more efficient than in the upper part of the post renal cava Anatomical studies of cavae blocked by emboli at various levels have shown clearly that the most important parts of the collateral circulation are the inflowing lumbar vessels which are seen at the main point of embolus occlusion (or even below it), to drain into the upper cava through channels in the thrombus The same studies likewise showed a negligible danger of embolism from propagated thrombus above such a low occlusion

Complete ligation of the inferior vena cava inevitably results in a dilation of the collaterals that is absent in a satisfactory partial occlusion Embolism via these dilated collaterals is well documented although passage of lethal sized emboli is rare, perhaps because the mouths of dilated collaterals seldom themselves dilate to more than 3 or 4 mm [14] Ligation certainly cannot be counted on permanently to protect against microembolism but experience shows that it is effective in the rare case where clinical episodes of pulmonary embolism occur after partial caval occlusion

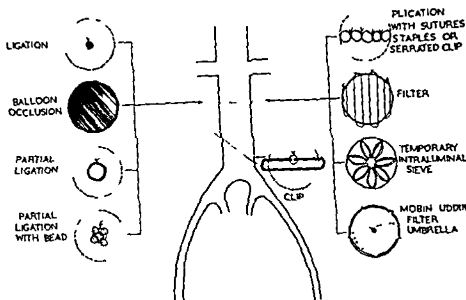


Fig 1 Diagrammatic representation of the various methods and devices used in the inferior vena cava to arrest lethal sized emboli (7 5 mm diameter or larger)

Patients who are suffering uncontrolled pulmonary embolism but are unfit for operation may be tided over the danger period by the transvenous insertion of various devices

Safe simplest and effective is the Eichelter sieve [5] quickly fabricated from easily available plastic tubing and introduced from the groin Partial caval occlusion by clip is advisable after a few days at the time of its removal

Simple permanent but completely occlusive is the balloon device of Hunter and associates The umbrella filter of Mobin Uddin also permanent is more complex sometimes dangerous may become dislodged and has very small channels prone to blockage by small emboli

Results of partial caval occlusion by clip

Twelve years experience indicates that clips provide continuing and probably permanent protection against fatal embolism The price of such protection is an increased incidence of peripheral venous thrombosis in the postoperative period with persistent new leg swelling in about one in five of the patients so treated Usually this swelling is easily controlled Two out of 55 patients followed up for a minimum of five years suffered venous claudication the most severely affected being a senior physician who claudicated on hills but enjoys a normal active social life Most clips retain patency but the majority of the patients with bilateral swelling had caval blocks whereas only one out of five patients with unilateral swelling had such a block

Caval blocks are almost always the result of impacted emboli The incidence of these emboli and the causative peripheral thrombophlebitis are certainly increased by partial caval occlusion The reason for this has been obscure the clips used in this series with a gap measuring 5 5 mm by 2 5 cm produced no measurable pressure differential Significant wave damping was noted however and since inferior vena caval blood flow is markedly pulsatile (personal observation with a 2 MHz ultrasonic Doppler haematachograph) it seems likely that pulsatile flow is an important factor in maintaining venous patency in the femoro iliac regions and that the smoothing out of this flow favors thrombosis

Mortality

In reasonably skilled hands partial caval occlusion is no more dangerous than other intra abdominal operations Reported mortality figures are often misleading because they include numbers of desperately ill patients often subjects of pulmonary embolectomy

In the author s personal series of 517 mainly elective partial caval occlusions there were four deaths attributable to the surgery The only intraoperative death was in a patient who suffered a massive pulmonary embolism and a

few hours later a perforated duodenal ulcer Two later deaths followed septic complications of peripheral thrombophlebitis, one other patient died when an embolus passed through a faulty clip which had widened to give an 8 mm gap

There is no doubt that in appropriate cases the application of a caval clip can be life saving Moreover it is a relatively simple and speedy technique, soon learned and well within the scope of any District General Hospital To date it has not gained wide popularity possibly because of confusion with caval ligation, or because its dangers have been exaggerated

But viewed in the light of its proven high effectiveness in protecting against pulmonary embolism, it surely deserves a recognized place in our armamentarium against pulmonary embolism, and where anticoagulants fail or are inappropriate it finds its clearest indications

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Clinical communications

Non specific aorto arteritis in Singapore with special reference to hypertension

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L K A Tan MB DMRD FRCR**
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Aorto arteritis has recently emerged as a distinct disease entity with involvement of aorta and its major branches by a non specific inflammation of unknown etiology Because of its protean manifestations it was formerly known as Takayasu s disease pulseless disease brachial arteritis arteritis of aorta in young women young female arteritis aortic arch syndrome reversed coarctation syndrome of occlu ion of supra aortic trunks and many other exotic names Each of these names emphasized a different mode of clinical presentat on of this disease and some of them stressed the predominance of female patients affected by this disease Since any segment of the aorta and any of its major branches might be affected Schrire and Asherson in 1964 coined the term arteritis of the aorta and its major branches Recently Sen proposed that it should be most appropriately and conveniently named non specific aorto arteritis [1] Though the distribution of this disease is worldwide and does occur occasionally in the Western world [1] it is more prevalent in Japan India and Southeast Asia In Singapore Danaraj and Wong first reported two cases in 1959 and subsequently another nine cases of aorto arteritis presenting with hypertension as a result of renal arteries involvement [4] The purpose of this paper is to describe a series of 48 cases seen by us in Singapore to empha ize the protean nature of the disease and to point out the frequency of hyper tension as a manifestation

Clinical material

The criteria for the diagnosis of non specific aorto arteritis are vascular bruits over the neck abdomen and inter scapular area unequal or absent neck or limb pulses especially in children and young adults and the absence of evidence of other disorders like syphilis systemic lupus erythematosus and polyarteritis Radiological examination is essential for the diagnosis Thoracic and/or abdominal aortography was employed to confirm the diagnosis in 38 out of the 48 patients included in this series In the remaining 10 patients where no aortography was done the diagnosis was confirmed in seven of them by postmortem examination

The age sex and race distribution are shown in Table I The disease is more common in children and young adults and the majority of them (37 patients) were below 30 years of age The youngest was 7 years old and the oldest was 48 years old with a mean age of 23 years As in other series the disease affected predominantly the

From th Un rsity Departme t of Medicine S ngapore General Hosp tal, Sing pore

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Reprint request D P C Teoh, U rs ty Department of Medicin Singapore G ner l Hosp tal, S g pore 3

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few hours later a perforated duodenal ulcer Two later deaths followed septic complications of peripheral thrombophlebitis, one other patient died when an embolus passed through a faulty clip which had widened to give an 8 mm gap

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Fig 1 Constriction of aorta at the lower descending artery



Fig 2 Dilatation of the ascending aorta and the innominate artery with obliteration of both subclavian arteries

them had S gallop rhythm Though aortic incompetence was noted in four patients it was severe and hemodynamically significant in only one patient Mitral incompetence was encountered in two patients most probably secondary to congestive heart failure and presumably functional in nature Ischemic changes with S T segment depression and flattened or inverted T waves were found in the electrocardiograms (ECGs) of nine patients and coronary artery occlusion or narrowing in four patients was found during autopsy But no frank myocardial infarction was detected in any of our patients

Pulse abnormalities and vascular bruits Pulse abnormalities are characteristic of aorto arteritis because of frequent involvement of major branches of the aorta Weak or absent pulses were found to occur in 30 patients They were more common in the upper limbs and neck than in the lower limbs Left side pulses were more frequently affected than those of the right Lower limb pulses were affected in 11 patients in our series only one presented with intermittent claudication and gangrene of the leg There were some mild nutritional changes in others Vascular bruit was another characteristic feature of aorto-arteritis and was heard in 29 patients Abdominal bruits were the commonest and occurred in 22 patients Bruits over the neck were heard in 16 patients and over the chest in five others In 13 patients the bruits were heard at more than one site indicating the diffuseness of the lesions in aorto arteritis Difference in pulses and the presence of bruits over one or more arteries were the most useful signs in the diagnosis of aorto arteritis Unless examination for differential pulse and vascular bruits becomes part of the routine assessment of the patients examples of this disease would undoubtedly be missed or over looked

Angiographic studies Though the diagnosis of this disease can be often reached by careful clinical examination angiographic studies are essential to confirm the diagnosis and to outline clearly the type and extent of the lesion Abdominal aortograms were performed in 30 patients

Table I Age, sex and race distribution

Age (years)	Male	Female	Chinese	Malay	Indian	Total
0 9	0	1	1	0	0	1
10 19	6	12	16	2	0	18
20 29	6	12	13	2	3	18
30 39	3	6	7	1	1	9
40-49	0	2	1	1	0	2
Total	15	33	38	6	4	48

Table II Chief complaints

Symptom	No of cases
Dyspnea	9
Headache	9
Unequal pulses	8
Giddiness	5
Palpitation	5
Hemiparesis	5
Chest pain	4
Ankle edema	4
Hemoptysis	3
Syncope	3
Fits	2
Fever	2
Blurred vision	2
Intermittent claudication	1
Painful nodules	1
Ptosis	1
Abdominal pain	1
Sudden death	1

young females A total of 33 females were affected compared with 15 males in this series, giving a female to male ratio of 2 2 to 1 Among them there were 38 Chinese, 6 Malays, and 4 Indians It did not appear that any of the above races was affected more frequently than the others as the ratio corresponded quite closely to the composition of the various races in Singapore

Table II showed the chief complaints of our patients They were many and varied Chief complaints related to cardiac involvement were dyspnea palpitation chest pain and ankle edema complaints related to cerebral circulatory impairment were headache giddiness blurred vision, syncopal attacks and fits complaints related to circulatory disturbance of the extremities were unequal or absent pulses and intermittent claudication

Table III revealed the major modes of presentation among the 48 patients studied Thirty

Table III Major modes of presentation

Hypertension	33
Unequal pulses	30
Vascular bruits	29
Cardiac failure	14
Hemiparesis	5
Aneurysms	4
Optic atrophy	1

Table IV Signs of cardiac involvement

Cardiomegaly	21
Cardiac failure	14
S_3 gallop rhythm	11
Aortic incompetence	4
Mitral incompetence	2

three patients had hypertension 30 had unequal or absent pulses 29 patients developed vascular bruits at various sites 14 patients were in cardiac failure five patients presented with hemiparesis and four were admitted with aneurysms and died of rupture or dissection Optic atrophy was detected in one patient who complained of blurring of vision

Hypertension Hypertension was the commonest mode of presentations of aorto arteritis in this series of patients It occurred in 33 patients It was the predominant manifestation in 14 patients and it co existed with other manifestations in the remaining 19 patients The hypertension was mild (diastolic 90 to 104 mm Hg) in 12 patients moderate (diastolic 105 to 114 mm Hg) in 15 patients, and severe (diastolic 115 mm Hg or higher) in six patients One of them presented with hypertensive encephalopathy Abdominal bruits were heard in 22 patients with hypertension and subsequent abdominal aortogram revealed stenosis or occlusion of renal arteries in 25 patients with hypertension Two additional cases of renal artery stenosis were found on autopsy Therefore hypertension was renovascular in origin in 27 patients Two other patients were found to have coarctation of aorta to account for the hypertension whereas in the remaining four patients no obvious mechanism was found

Cardiac involvement The frequency of cardiac involvement in aorto arteritis in our series of patients was clearly shown in Table IV In 21 patients there was clinical evidence of cardiomegaly 14 of them developed cardiac failure and 11 of



Fig 1 Constriction of aorta at the lower descending artery



Fig 2 Dilatation of the ascending aorta and the innominate artery with obliteration of both subclavian arteries

them had S gallop rhythm Though aortic incompetence was noted in four patients it was severe and hemodynamically significant in only one patient Mitral incompetence was encountered in two patients most probably secondary to congestive heart failure and presumably functional in nature Ischemic changes with S T segment depression and flattened or inverted T waves were found in the electrocardiograms (ECGs) of nine patients and coronary artery occlusion or narrowing in four patients was found during autopsy But no frank myocardial infarction was detected in any of our patients

Pulse abnormalities and vascular bruits Pulse abnormalities are characteristic of aorto arteritis because of frequent involvement of major branches of the aorta Weak or absent pulses were found to occur in 30 patients They were more common in the upper limbs and neck than in the lower limbs Left side pulses were more frequently affected than those of the right Lower limb pulses were affected in 11 patients in our series only one presented with intermittent claudication and gangrene of the leg There were some mild nutritional changes in others Vascular bruit was another characteristic feature of aorto arteritis and was heard in 29 patients Abdominal bruits were the commonest and occurred in 22 patients Bruits over the neck were heard in 16 patients and over the chest in five others In 13 patients the bruits were heard at more than one site indicating the diffuseness of the lesions in aorto arteritis Difference in pulses and the presence of bruits over one or more arteries were the most useful signs in the diagnosis of aorto arteritis Unless examination for differential pulse and vascular bruits becomes part of the routine assessment of the patients examples of this disease would undoubtedly be missed or overlooked

Angiographic studies Though the diagnosis of this disease can be often reached by careful clinical examination angiographic studies are essential to confirm the diagnosis and to outline clearly the type and extent of the lesion Abdominal aortograms were performed in 30 patients



Fig 3 Aneurysms of the lower thoracic aorta and the abdominal aorta with an obliteration of right renal artery and superior mesenteric artery



Fig 4 Irregularities and dilatations of the abdominal aorta with bilateral occlusion of the renal arteries near their orifices Well developed collateral vessels fill the renal arteries later in the series The superior mesenteric artery is seen just above the aortic kink as a large dilated vessel occluded soon after its origin

and arch and thoracic aortogram were done in 25 patients The characteristic features of aorta in aorto arteritis were constriction (Fig 1), dilatation (Fig 2) aneurysm (Fig 3) irregularity (Fig 4) total occlusion (Fig 5), and lastly any of the above in combination (Fig 6) Table V shows the type, frequency and locations of aortic involvement It is worth noting that the abdominal aorta was affected more frequently than the thoracic aorta As for the thoracic aorta the descending portion bore the brunt of disease in 14 patients the arch of the aorta was affected in five patients whereas the ascending aorta was least affected with lesions in only two patients Table VI shows the frequency of involvement of the major arteries of the aorta by aorto arteritic process The renal arteries (Fig 7) and the subclavian arteries (Fig 8) were the most commonly affected ones Renal arteries were affected 39 times in 25 patients, out of whom 14 patients had bilateral renal artery involvement and the remaining 11 patients had either right or left renal artery disease

Laboratory investigation Mild anemia with hemoglobin of 9 to 12 Gm per cent was found in 16 patients, whereas moderate anemia with hemoglobin of less than 9 Gm per cent was found in three patients Leucocytosis was noted in 12 patients whereas erythrocyte sedimentation rate (ESR) was elevated in 30 patients In 12 of them the ESR was between 20 to 49 mm /hour in 15 of them it was between 50 to 100 mm /hour and only 3 patients had an ESR of more than 100 mm /hour Antinuclear factor and direct Coombs test were negative and lupus erythematosus cells were absent in all the patients however rheumatoid factors (R A) were positive in three patients Kahn test and VDRL test for syphilis were negative in all except in two patients which finding we believed was incidental None of them had an elevated serum cholesterol level Blood urea and electrolytes were all



Fig 5 Total occlusion of the abdominal aorta with extensive collateral formations

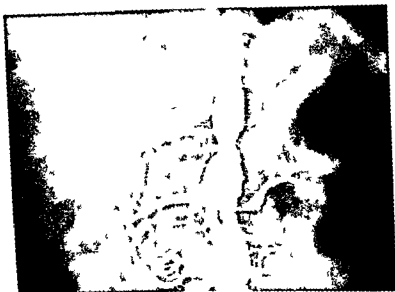


Fig 6 Irregularities constrictions and dilatations of the abdominal aorta with stenosis and post stenotic dilatation of the left renal artery There is also stenosis of the right renal artery origin clearly visible through the superior mesenteric artery

within normal limits Electrocardiograms showed left ventricular hypertrophy in 21 patients and ischemic changes with S T segment depression and flattened or inverted T waves in nine patients Chest radiograms showed cardiomegaly in 20 patients pulmonary congestion in six patients calcification of the aorta in eight patients and dilatation of the aorta in three patients

Progress Five patients were treated with oral corticosteroids and the response was equivocal It did not appear to arrest the slow progress of the disease Out of the 33 patients with hypertension nephrectomy was done in three patients with favorable response in two In both of them blood pressure became normal The other 30 patients were treated medically with hypotensive agents such as chlorathiazide guanethidine methyl

Table V Angiographic presentations

	Abdominal aorta	*Thoracic aorta*
Constriction	10	8
Dilatation	6	9
Aneurysm	1	2
Irregularity	7	3
Combination of the above	5	1
Total occlusion	2	0

Table VI *Involvement of major branches of* aorta

Innominate	5
Carotids	13
Subclavians	32
Celiac	5
Superior mesenteric	9
Renal	39

Table VII Causes of death

Cardiac failure	4
Dissecting aneurysm	3
Ruptured *aneurysm*	1
Cerebral hemorrhage	1
Sudden death	1

dopa debrisoquin sulfate and propranolol at conventional dosages The control of blood pressure was *satisfactory in 21 patients but poor in* nine patients The severity and the treatment of hypertension played an *important part* in the prognosis and the mortality of the patients with aorto arteritis This was quite well shown by the fact that five patients died as a result of uncontrolled and severe hypertension four of them from heart failure and one of them from cerebral hemorrhage (Table VII) Other causes of death included dissecting aneurysms ruptured aneurysm and sudden death Though the occurrence of aneurysms *of the aorta* and its main branches in aorto arteritis had increasingly been recognised we were *surprised to note that four out of* 10 deaths were as a result of dissecting and ruptured aneurysms of the aorta The diagnosis of non specific aorto arteritis was confirmed on postmortem examination in all four cases Therefore aneurysms should be regarded as an important manifestation of this disease entity, especially from the standpoint of prognosis As rupture or dissection may occur surgical intervention *should be considered* whenever possible At the time of review there were 14 patients who were lost *to follow up Among the 24 patients* who survived, 12 patients were still alive from 1 to 5 years later, seven were alive *from 6 to 10* years *later, and the remaining five were alive from 11 to* 18 years later The longest survival was 18 years This indicated that the disease process was slow *and chronic and the prognosis depended on the* nature and the degree of involvement of the vessels and the severity of hypertension

Discussion

The occurrence of hypertension in aorto arteritis was *first pointed out by Giffin in 1939 but it was considered unusual by* Kalmansohn and Kalmansohn[9] in 1957 However, in 1961 Ask *Upmark[10] showed that 29 out of 60 cases studied* had increased blood pressure giving an incidence of 48 per cent In Singapore it was Danaraj and co workers[5,6] who *first brought to our attention* in 1959 that hypertension was not an uncommon manifestation of aorto arteritis[5,6] This was later confirmed *by Ooi and colleagues[11] in 1971 who* showed that aorto arteritis contributed to 4 per cent of the 127 young hypertensive patients under study in Singapore *In our present series of 48* patients 33 patients suffered from hypertension giving an incidence of 69 per cent This incidence was much higher than the 48 per cent reported by Ask Upmark[10] among *Europeans and the 42 per* cent reported by Schrire and Asherson among South Africans However it was quite similar to the incidence of 64 per cent reported recently by workers in China[1] It would therefore appear that hypertension was a far more *common manifestation* of aorto arteritis among the Asians and especially among the Chinese

The commonest cause of *hypertension in aorto* arteritis in our series is renovascular *with renal* artery stenosis or occlusion occurring in 27 cases (85 per cent) *Hypertension caused by coarctation* of aorta was found in two patients only In the remaining four patients with hypertension the mechanism *was not* obvious though it was possible that it might be due to the loss of elasticity of aorta as a result of diffuse aortic involvement *as suggested* by Ask Upmark[10] Though hypertension is usually due to renal artery involvement one must bear in mind that *the occlusion of the renal artery alone does not* always insure that hypertension is on a renal



Fig 7 Stenosis of the left renal artery with long smooth constriction of the mid abdominal aorta



Fig 8 Absent left subclavian artery with dilatation of innominate artery The right common carotid artery shows dilatations and irregularities and the left common carotid and the right subclavian artery are occluded as well

ischemic basis Other factors like cerebral ischemia and involvement of baroreceptors in the affected aorta and/or carotid arteries must be considered as possible mechanisms of hypertension in such patients The renal arteries were affected mainly at the ostia or the first parts hence differentiating them from other causes of renal artery stenosis like fibromuscular hyperplasia The frequency of renal artery involvement is much greater than a comparable series reported by Ueda [3] in Japan who showed that out of 42 cases of aorto arteritis 12 patients had angiographic evidence of renal artery stenosis and two other patients revealed renal involvement on autopsy giving an incidence of 34 per cent The frequency of renal artery involvement has only recently been appreciated even when the arch of aorta appears to bear the brunt of the disease When the upper abdominal aorta is involved the renal arteries are almost universally affected and hypertension was a constant finding in most of our patients Therefore renovascular hypertension should be regarded as a predominant feature of this disease The possibility of renovascular hypertension as a manifestation of aorto arteritis should always be considered in the diagnosis of hypertensive patients in Singapore especially if the patient is a young female since it greatly influences the prognosis of the disease

Summary

Aorto arteritis has recently emerged as a distinct disease entity with involvement of aorta and its major branches by a non specific inflammation of unknown etiology Though the distribution of this disease is worldwide it is more prevalent in Japan India and South east Asia This paper describes a series of 48 cases seen in Singapore and emphasizes the protean nature of this disease Though modes of clinical presentation were many hypertension appeared to be the commonest as it occurred in 33 patients giving an

incidence of 69 per cent This incidence was much higher than the 48 per cent reported among Europeans and 42 per cent reported among South Africans It would therefore appear that hyper tension was a far more common manifestation of aorto arteritis among Asians The commonest cause of hypertension in aorto arteritis in this series was renovascular, with renal artery stenosis or occlusion occurring in 27 cases (85 per cent) The frequency of involvement of the renal artery is much greater than the 34 per cent reported by the Japanese Therefore renovascular hyperten sion should be regarded as a predominant feature of aorto arteritis in Singapore

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Myocardial infarction in the Black population of South Africa: Coronary arteriographic findings

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Among the various racial groups of South Africa there exists a striking difference in the prevalence of myocardial infarction. The White population is afflicted to a degree which approximates that of the U.S.A., but in the age group between 25 to 44 years the incidence in the South African White may be the highest in the world. In contrast, the Black population is almost immune to the disease.

Estimates of the prevalence of ischemic heart disease in the Black population have been derived from necropsy studies but predominantly from extensive electrocardiographic surveys.[1-6] There has, however, been no documentation of the coronary angiographic findings in Black patients who manifest clinical and electrocardiographic evidence of myocardial infarction. This paper reports our findings in 13 such patients who underwent this investigation. Our findings suggest that occlusive coronary atherosclerosis in the Black population may be even less common than suggested by previous electrocardiographic evidence.

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Subjects and methods

This cardiac unit is the only referral service for coronary angiography in the Province of Natal. It therefore serves a population comprised of 1,132,897 Blacks, 523,918 Whites, 439,570 Asiatics, and 68,093 Mulattoes.

Since 1968 we have performed a total of 800 coronary angiograms of which 13 were on Black and 787 on White patients. These Black patients form the subject of this report where we detail the findings at coronary arteriography and, utilizing the admission figures to the general medical wards of our referring hospital, comment on the prevalence of myocardial infarction.

All 13 patients were pure Black. All had experienced previous episodes of acute transmural myocardial infarction diagnosed on the basis of a characteristic clinical picture supported by unequivocal electrocardiographic findings of pathological Q waves and elevated ST segments. Serum transaminase (glutamic oxalacetic or glutamic pyruvic) or lactic dehydrogenase levels were raised in all patients. Serology for syphilis was always negative. In none was there evidence of dissecting aortic aneurysm, viral myocarditis, or collagen disease. Serum cholesterol levels were measured in 11 patients and in seven a complete lipoprotein analysis was available. An enquiry into their socioeconomic status, dietary habits, and family history was made.

Coronary arteriography was performed using the Judkins technique. Films were exposed at 64

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Table I Clinical, electrocardiographic, and coronary angiographic data on 13 Black patients with transmural myocardial infarction

Patient no and age		Sex	Blood pressure	Cholesterol	ECG* location of infarct	No of coronary arteries affected	Mitral valve	Occupation
1	50	M	140/80	168	Inferior	3	Normal	Policeman
2	38	M	100/70	228	Anterior	2	Normal	Manual labourer
3	48	M	100/70	288	Anterior	2	Normal	Manual labourer
4	39	M	110/80	264	Inferior	2	Normal	Manual labourer
5	36	M	140/90	201	Inferior	1	Normal	Manual labourer
6	45	M	140/90	262	Inferior	1	Normal	Manual labourer
7	64	M	110/70	166	Anterior	3	Normal	Ex manual labourer
8	46	F	100/70	?	Anterior	2	Normal	Housewife
9	35	M	120/70	?	Inferior	2	Normal	Policeman
10	40	M	110/60	200	Inferior	1	Normal	Manual labourer
11	32	M	140/90	209	Anterior	Nil	BMLS*	Manual labourer
12	27	M	120/80	201	Anterior	Nil	BMLS	Manual labourer
13	51	M	130/70	222	Anterior	Nil	Normal	Manual labourer

BMLS = Billowing mitral leaflet syndrome ECG = electrocardiogram

frames per second using a 6 inch camera with an over framing lens Left ventricular function was assessed angiographically in the right anterior oblique view following the injection of 50 c c of 70 per cent Urografin The left ventricular end diastolic pressure and dp/dt were also available

Results

The material was divided into two groups on the basis of the coronary arteriographic findings (Table I)

Group A Angiographically abnormal coronary arteries (Cases 1 to 10)

Age The mean age was 44 (± 8 7 SD) years

Sex Nine were male and one was female

Occupation Apart from two who were policemen and the one female who was unemployed all were manual laborers

Blood pressure This was normal in all patients

Serum cholesterol This varied from 166 to 288 mg per cent mean 222 mg per cent

Left ventricular angiograms There were always abnormal and revealed areas of hypokinesis dyskinesis or aneurysm In three the infarction was anterior and in three inferior in two patients there was generalized hypokinesis or ischemic myopathy The remaining two patients each had an anteroseptal aneurysm

Coronary arteriography Significant lesions were considered to be present when 75 per cent of the lumen was obstructed Three patients had single vessel disease involving the right coronary artery Five patients had diffuse disease in two vessels and the remaining three patients had triple vessel disease

Left ventricular end diastolic pressure was elevated above 14 mm Hg in all but two patients

Group B Angiographically normal coronary arteries (Cases 11 to 13)

Age The mean age was 36 7 years

Sex All were male

Occupation All were manual laborers within the low income group

Blood pressure This was within normal limits

Serum cholesterol These were 209 201, and 222 mg per cent

Left ventricular angiograms Two of these patients had evidence of prolapse of the posterior leaflet of the mitral valve and left ventricular contractility was normal The third patient with an anterior ventricular aneurysm did not have prolapse of the mitral valve

Coronary arteriography Angiographically the coronary arteries were considered normal in all three patients

Left ventricular end diastolic pressure This was normal apart from the patient with the aneurysm in whom it was 15 mm Hg

Prevalence of ischemic heart disease An estimate of the clinical prevalence of ischemic heart disease among the Black population of Natal may

be made from statistics available from our referring hospital During 1976 10 553 Black adult patients were admitted to the general medical wards Among these there were five cases with unequivocal electrocardiographic and enzymatic evidence of transmural myocardial infarction providing a prevalence rate of only 0 05 per cent of medical admissions However this figure should be treated with reserve since three of these five patients are included in our series and in one the coronary arteries were found to be angiographically normal In the remaining 10 patients of our series studied before 1976 the coronary arteries were found to be normal in another two

Discussion

An accurate assessment of the prevalence of ischemic heart disease is difficult to obtain National vital statistics are dependent upon accurate death certification and take no account of the prevalence in the living A full electrocardiographic investigation is very helpful in establishing the diagnosis of ischemic heart disease provided the diagnostic criteria are rigid and an adequate sample of the population at risk is available for study Numerous such studies have demonstrated the striking immunity of the South African Black population to ischemic heart disease but there has been some variation in the reported frequency in the clinical series (Table I) Thus Schwartz and colleagues in an analysis of 30 cases among 417 000 medical admissions to Baragwanath Hospital for the period 1951 to 1961 determined a prevalence rate of 0 01 per cent In comparison to control groups their 30 cases of myocardial infarction showed a marked predominance of males with a high incidence of hypertension diabetes and obesity In addition these subjects were engaged in the more skilled occupations and had adopted a westernized life style In a later study at the Johannesburg General Hospital in 1970 Seftel and Kew found a prevalence rate of 0 6 per cent among 3 000 admissions to the medical wards These authors concluded that the prevalence had increased as a result of westernized life style in an urban environment A large proportion of their patients were cooks leading a sedentary life and they were frequently diabetic hypertensive and had elevated serum lipids In both these studies autopsy confirmation was available in 21 of the 54 cases

Table II The racial prevalence of ischemic heart disease from various parts of South Africa

Author	*Area*	*Date*	*No of cases*	*IHD %*	*Race*
Schrire	Cape Town	1970	25,896	30	Whites
Schrire	Cape Town	1970	4 485	1 4	Black
Schwartz et al	Transvaal	1958	2 5	0 4	Black
Seftel et al	Transvaal	1963	417 000	0 01	Black
Seftel and Kew	Transvaal	1970	3 600	0 6	Black
Cosnett	Natal	1962	1 000	0 6	Black
Powell and Wright	Natal	1965	2 0	0	Black
Present series	Natal	1975	10 553	< 0 05	Black†

Autopsy confirmation in 1 of the 54 cases in both studies
†Coronary angiography in 3 of the 5 patients.

In Cape Town Schrire initially used rigid electrocardiographic criteria similar to those of Rose and Blackburn[7] in the diagnosis of myocardial infarction Subsequently less stringent criteria were adopted and the diagnosis was made without the presence of pathological Q waves[1] Among 4 485 patients a diagnosis of ischemic heart disease was considered present in 1 4 per cent a figure much higher than reported from other centers However autopsy confirmation or coronary arteriography was not available in this series

Confirmation of the rarity of ischemic heart disease in the Black population is available from necropsy data Thus, sudden death in Black patients is nearly always a result of cardiovascular syphilis[8] Necropsy evidence of occlusive coronary atherosclerosis and myocardial infarction in subjects over the age of 30 has been found in only 1 5% of autopsies by Becker[8,9] 2 2% by Higginson et al[10] and 2 2% by Kallichurum

To our knowledge there has been no report on the coronary arteriographic findings in Black patients in whom the diagnosis of myocardial infarction has been made electrocardiographically In three of the 13 Black patients investigated by us the coronary arteries were found to be angiographically normal We believe therefore that our prevalence rate is in fact less than 0 05 per cent and that the figures provided by other workers based on electrocardiographic evidence in the absence of autopsy confirmation or coronary arteriography are similarly too high

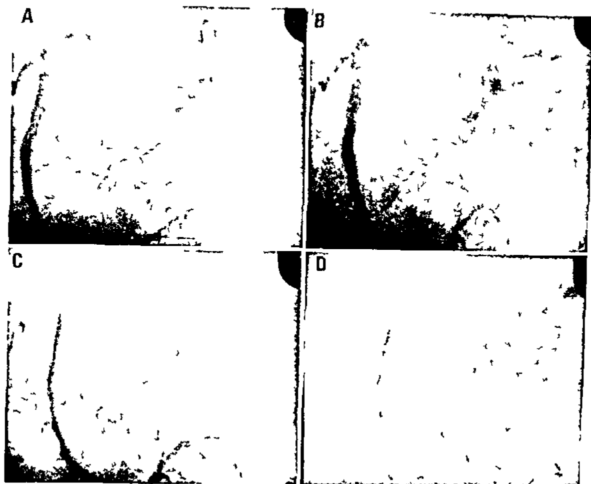


Fig 1 Selective right coronary arteriogram left anterior oblique view from a patient not included in this series At the start of the injection *(A)* the right coronary artery is somewhat irregular but there is no significant stenotic lesion Following withdrawal of the catheter there is progressive diffuse spasm of the entire right coronary artery almost to the point of obliteration *(B C and D)*

Our findings suggest that a disproportionate number of our Black patients with myocardial infarction have angiographically normal coronary arteries It is interesting that in our total experience with coronary arteriography since 1968 there have been only three examples of angiographically normal vessels in 787 angiograms performed on White patients However our White patients are almost invariably referred for this investigation because of angina pectoris refractory to beta blocker therapy whereas the Black patients were referred electively for academic reasons because of the rarity of ischemic heart disease It is possible that more frequent investigation of White patients who have made an uncomplicated recovery from myocardial infarction would reveal more cases with angiographically normal vessels Our three White patients in fact fell into this category and were investigated because they were young and both they and members of their families had non ejection clicks they were shown to be examples of the billowing mitral leaflet syndrome

Previously we have commented upon acute myocardial infarction with normal coronary arteries as a possible manifestation of the billowing mitral leaflet syndrome[1] The electrocardiograms of these patients were characterized initially by pronounced elevation of the ST segments as occurs in Prinzmetal s angina Coronary artery spasm provoked by the billowing mitral leaflet was considered as a possible cause Alternatively fibrin emboli emanating from the redundant mitral leaflets could be responsible and this could also account for major ischemic neurologic disturbances also associated with mitral leaflet prolapse[11] In two of our Black patients in this series with normal coronary arteries there was also angiographic evidence of a billowing posterior leaflet and in one of these two a non ejection click had been detected

There is now considerable direct and indirect

evidence that coronary artery spasm may be responsible for myocardial ischemia Several reports document the presence of normal coronary arteries in patients with variant angina and with documented myocardial infarction and angiographically demonstrable segmental left ventricular dysfunction Coronary artery spasm has been noted with both angiographically diseased and with normal vessels [8,9] Whereas proximal coronary artery spasm has occasionally been seen during coronary arteriography and is thought to be a result of mechanical stimulation by the catheter diffuse spasm may be induced by the administration of ergonovine maleate and has been observed during withdrawal from nitroglycerine exposure [8] We have observed spontaneous progressive diffuse spasm of a coronary artery following withdrawal of the injecting catheter from the vessel (Fig 1)

In our 10 patients with occlusive atherosclerosis the angiographic pattern of lesions was similar to that seen in Whites Three patients had single five had double and three had triple vessel disease The series is small but the clinical profile appears to be at variance with the characteristics observed by the Johannesburg workers Thus the majority were manual laborers who were not diabetic hypertensive or obese and could not be classified as westernized in their life style The majority were however also young males Their mean serum cholesterol level was 222 mg per cent a figure similar to those with angiographically normal coronary arteries and a significant proportion of the urban Black population Thus Walker found that in the age group 30 to 39 years a serum cholesterol level above 220 mg per cent was present in 55 per cent of Whites 25 per cent of urban and 10 per cent of rural Blacks

Hypertension is common in the urban Black and is frequently accompanied by cerebrovascular and renal complications Yet in a study of 500 patients over a period of 13 years Seedat and Reddy found no examples of myocardial infarction complicating the disease Even in the presence of severe aortic atherosclerosis in Black subjects involvement of the coronary and peripheral vessels is rarely seen The immunity of the Black population to ischemic heart disease therefore remains an enigma Our estimated prevalence rate of less than 0 05 per cent of medical admissions suggests that the disease is in fact no more frequent than it was 15 years ago despite the effect of urbanization Possibly a new look at mechanisms which protect the arterial wall and prevent the development of atherosclerosis in the face of other known accelerating factors may be rewarding

Summary

Thirteen Black patients who had classic electrocardiographic evidence of myocardial infarction supported by changes in serum enzymes were investigated by coronary arteriography Ten of these had occlusive atherosclerosis and in none of these did the associated risk factors such as hypertension or diabetes appear to be operative and most were manual laborers Their mean serum cholesterol measurement was found to be 222 mg per cent a value which is found in 25 per cent of the urban Black population In the remaining three patients the coronary arteries were found to be angiographically normal and two of these were associated with the billowing mitral leaflet syndrome it is postulated that their myocardial infarction was a result of coronary spasm or a consequence of fibrin emboli emanating from the redundant mitral leaflets Based on statistics from our major referring hospital it is estimated that the prevalence rate from myocardial infarction among general admissions to a medical ward is less than 0 05 per cent a figure lower than previously reported by clinico electrocardiographic studies It would appear that the prevalence of this disease has not increased over the last two decades and the immunity of the Black population is unexplained

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Four year follow up of Black schoolchildren with non ejection systolic clicks and mitral systolic murmurs

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In 1972 a survey was undertaken by this unit on Black schoolchildren in the South Western Townships (Soweto) near Johannesburg with the primary objective of determining the prevalence of rheumatic heart disease in that population A total of 12 050 children randomly selected to represent a school population of about 99 000 were auscultated by 10 trained or trainee cardiologists Rheumatic heart disease was detected in 80 children yielding an optimally weighted prevalence rate of 6 9 per thousand One hundred and sixty eight children yielding an over all prevalence rate in the sample school population of 14 per thousand had a non ejection systolic click (NESC) a late systolic murmur or both [2] We had thought this a high prevalence of these auscultatory features and had wondered whether many were not suffering from early rheumatic heart disease A follow up study of these 168 children was clearly indicated

The present study was therefore undertaken with the primary objective to determine by clinical examination and careful auscultation the current status of the 168 children or as many as could be traced after a four year period during which they had received no prophylaxis again t rheumatic activity The investigation also provided an opportunity to examine equally carefully the same number of age and sex matched control Black schoolchildren in order to reassess the prevalence of NESCs and mitral systolic murmurs in this population group

Methods

The subjects were visited personally by one of us (M C) at their homes in Soweto and where possible the proposed investigation was discussed with both the children and their parents Appointments were made for examination at Baragwanath Hospital during February 1976 Of the 168 children who had had an NESC or late systolic murmur in 1972 the record files of three had been mislaid Six children could not be traced four were seen in their homes and appeared well but refused examination and 16 were reputed to be well but were at boarding school outside the Johannesburg area Examination of the 16 boarding school children had been planned for July 1976 but due to civil unrest and rioting in Soweto this was not possible Nevertheless eight of the 16 children did attend Baragwanath Hospital during July 1976 and were examined for us by two cardiologists

One hundred and thirty nine subjects (91 females 48 males) were thus available for examination during February 1976 together with the same number of age and sex matched controls The ages ranged from six to 21 years with a mean age of 15 years The cardiovascular system was examined by J B B who at all times was unaware as to whether the child was a 1972

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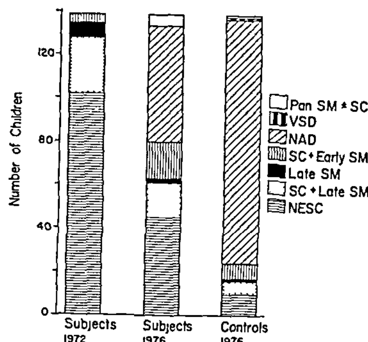


Fig 1 Histogram showing the auscultatory features of the 139 subjects in 1972 and on re auscultation in 1976 together with the auscultatory features of the 139 control children For full description see text *Pan SM ± SC* = pansystolic murmur ± non ejection systolic click *VSD* = ventricular septal defect *NAD* = no abnormality detected *SC + Early SM* = non ejection systolic click and early systolic murmur *Late SM* = late systolic murmur *SC + Late SM* = non ejection systolic click and late systolic murmur *NESC* = non ejection systolic click

subject or a 1976 control Any abnormality of the thoracic cage was noted A 12 lead electrocardiogram was recorded by a technologist, but was not seen by the examiner The electrocardiograms were later reported by J B L who, in turn, was unaware of the auscultatory findings and to which group the child belonged

All children were auscultated in the supine left lateral erect and squatting positions The examination was never completed in less than three minutes usually took five to eight minutes and occasionally lasted 15 minutes or longer Auscultation was thus performed in more detail than is customary for a routine check or for the elucidation of a systolic murmur and certainly more carefully than during our 1972 study The findings were documented to describe all sounds murmurs and clicks their nature and intensity as well as the site at which they were heard and any alterations with changes in posture The NESCs were classified into three groups (1) Those that were easily heard and were usually loud (2+) (2) Those that were also definitely present but were soft and not as easily heard (1+) (3) Those that were possibly present having been heard for a few beats and not infrequently after a change in posture, but which could not be confirmed on further or repeated auscultation Children in this latter group, of whom there were as many as 16 6 per cent in the controls and 13 7 per cent in the subjects, are included in our analysis as normal on auscultation

Results

Subject group The auscultatory features of the 139 subject children in 1972 are shown in Fig 1 which also illustrates the status on re examination in 1976 One hundred and two children had had an isolated NESC 26 a NESC with an associated late systolic murmur seven an isolated late systolic murmur and four a NESC with an early nonpansystolic murmur, thought to denote mitral regurgitation In 1976, 45 children had an isolated NESC 16 a NESC and late systolic murmur two an isolated late systolic murmur, 16 a NESC and early systolic murmur, five had a pansystolic murmur of whom three had an associated NESC and as many as 55 (39 5 per cent) were passed as normal In 33 subjects the NESC was 1+ and in 47 it was classified as 2+ In only nine of the 80 subjects with a NESC was the click first heard or only heard in a position other than recumbent Only one of the five children with a pansystolic murmur had moderate mitral regurgitation and that child also had a markedly depressed sternum The remaining four children with pansystolic murmurs were assessed as having mild mitral regurgitation In one of the latter the murmur was pansystolic in the standing position only

Fig 2 shows the changes in the auscultatory features of the main subdivisions of 1972 as found on re auscultation in 1976 The 55 children now found to be normal came from each of the four subdivisions namely 44 of 102 with isolated NESCs (43 per cent) eight of 26 with NESCs and late systolic murmurs (30 7 per cent) two of seven with isolated late systolic murmurs (28 5 per cent) and one of four with a NESC and early systolic murmur (25 per cent) Furthermore there was no specific trend as each subdivision on re auscultation showed a whole spectrum of auscultatory features

Of the 16 children at boarding school eight (six female) were examined by two cardiologists at

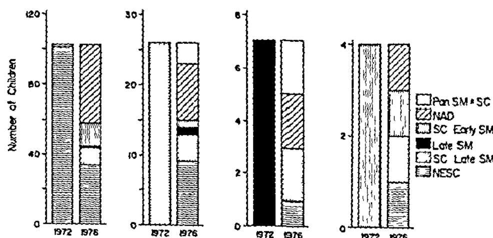


Fig 2 Histogram showing the breakdown in each category of the auscultatory features of the subject group in 19 6 as compared to those present in 197. For full description see text

Baragwanath Hospital during July 1976 No deterioration was found in any while one was assessed as normal

Control group The auscultatory features detected in the 139 age and sex matched controls are also shown in Fig 1 One hundred and thirteen were normal and one had the typical auscultatory features of a small ventricular septal defect One child had an isolated late systolic murmur and another had a pansystolic murmur of mitral regurgitation in the standing position without an associated NESC Twenty three children had NESCs 13 of whom had associated mitral systolic murmurs The NESC was assessed as 2+ in six children and 1+ in the remaining 17 In only two of the 23 was the NESC present or first heard in a position other than recumbent

Thoracic cage deformities Twenty-eight of the 139 subjects were found to have a narrow antero posterior chest diameter and 16 of these had a NESC (57 1 per cent) Seventeen in the control group had a narrow chest diameter seven of whom had a NESC (41 2 per cent) The prevalence of NESCs in the subject and control groups without a chest deformity was 57 6 per cent and 13 3 per cent respectively

Electrocardiograms ST and T wave abnormalities were detected in two subjects and two controls The typical pattern of inferior ischemia was present in the two subjects both of whom had a NESC One control assessed as normal on auscultation had deep T wave inversion from V to V_3 whereas the other who had a NESC and early systolic murmur showed the pattern of inferior ischemia together with T wave inversion from V to V A child in the subject group with a NESC and a late systolic murmur had a wandering atrial pacemaker with nodal escape beats Another subject passed as normal on auscultation in 1976 had occasional supraventricular ectopic beats and one premature ventricular contraction

Discussion

The results of this blind controlled study have yielded meaningful and to us somewhat surprising information on the prevalence of NESCs and mitral systolic murmurs in Black schoolchildren Of the 139 controls examined 23 (16 5 per cent) had a NESC and if the two with isolated mitral systolic murmurs are included 25 (17 9 per cent) had auscultatory features compatible with mitral valve prolapse A very high prevalence in normals has however been reported in other recent studies Markiewicz and colleagues in an investigation of 100 healthy female volunteers found a 17 per cent prevalence of NESCs and/or late or mid to late systolic murmurs on phonocardiograms recorded supine in the upright position or after inhalation of amyl nitrite Ten women had both auscultatory and echocardiographic evidence of mitral valve prolapse while 18 others had either echocardiographic or phonocardiographic findings suggestive of the mitral valve abnormality Procacci and co workers reported a prevalence of 6 3 per cent (74 of 1169 adult

females) on auscultation and mitral valve prolapse was confirmed using echocardiography in 60 of the 74 women Brown and associates[5] found echocardiographic evidence of prolapse in 6 per cent of 520 women with no history of heart disease These surveys suggested a much higher prevalence of mitral valve prolapse than had been reported previously either from our own laboratory[1] or by others The more than tenfold increase in prevalence detected among the 139 controls in our present study as compared to the larger survey in 1972[1] requires explanation It may partly be accounted for by the fact that only 10 per cent of the 12 050 children had been postured auscultation was necessarily hurried, the primary objective was the detection of rheumatic heart disease and some of the auscultators were relatively inexperienced In the present investigation on the other hand auscultation was detailed, prolonged, and undertaken in quiet and comfortable surroundings by an experienced auscultator who was listening specifically for these auscultatory features Had echocardiography been performed it is possible that more instances of mitral valve prolapse would have been detected since the entity of silent prolapse is accepted by some workers [10]

The significance of such a high prevalence rate of these auscultatory features in apparently normal children and young adults is uncertain at the present time and in some instances may represent a normal variant [3] In view of this and the rarity of infective endocarditis in subjects who have not taken prophylaxis [4] there is some doubt as to whether prophylaxis is indicated in all cases Infective endocarditis has indeed supervened in patients with an isolated NESC [11 12] but it is now apparent that this complication is rare in relation to the high prevalence of the physical sign Although we previously advised prophylaxis[13 14] in all patients with an isolated NESC this is often impracticable and may be unnecessary Perhaps prophylaxis against infective endocarditis should be recommended only in instances where there is a constant mitral systolic murmur

The etiology of the mitral valve abnormality in the subject group is not known Although we had suggested that mild rheumatic heart disease was the probable underlying cause in a large proportion of the 168 children with NESCs and late systolic murmurs detected in that survey their subsequent course has not supported our postulate During the four years since the survey was completed none of the subjects was on prophylaxis against rheumatic fever yet 55 were normal on re examination and only one showed significant deterioration That patient has a markedly depressed sternum and may represent a forme fruste of the Marfan syndrome Four others may have deteriorated slightly in that they now have soft pansystolic murmurs In all of the four the mitral regurgitation was assessed as mild It is probable that the majority of both subjects and controls with the auscultatory features of a NESC and/or early late or pansystolic murmurs of mitral regurgitation have 'idiopathic pro lapse, albeit mild, and that a few will in time manifest features of the specific billowing mitral leaflet syndrome [15 16] Electrocardiographic abnormalities compatible with the syndrome were present in a small number in both groups and thoracic cage abnormalities which are a recognized accompaniment of mitral valve prolapse,[17 18] were slightly more common in the subject group

The results of this four year follow up of the subject group is in keeping with the generally benign prognosis[4 9 14 19 20] of the billowing mitral leaflet syndrome Reassessment at a later date of both groups would clarify the natural history of these auscultatory features in young urban Blacks

Summary

In 1972 we conducted a survey of 12 050 urban Black schoolchildren and detected 168 (prevalence rate of 14 per 1 000) with a non ejection systolic click (NESC) a late systolic murmur or both The etiology of the mitral valve abnormality was unknown but we considered that a significant proportion might have early rheumatic heart disease

The auscultatory features four years later of 139 of the original 168 subjects as well as those of 139 age and sex matched controls are presented in this study No cardiac abnormality was detected in as many as 55 of the subjects Five children now had pansystolic murmurs but the mitral regurgitation was assessed as mild in four Twenty five (17 9 per cent) of the controls 23 of whom had NESCs had auscultatory features compatible with mitral valve prolapse

These findings do not support our earlier

suggestion that a large number of the 1972 subjects have mild rheumatic heart disease The results are in accord with other studies which have indicated that auscultatory features compatible with mitral valve prolapse are common in normals and also that the prognosis of the specific billowing mitral leaflet syndrome is generally benign

We thank Dr P J Beukes Medical Superintendent Baragwanath Hospital for his co operation We are indebted to Dr A Bakst and Dr D M Bramwell-Jones for examining the boarding school children and to Miss P A Palfrey Miss K C Haverley Miss W Khonzaphi and Mrs I N Thebehali for technical and secretarial assistance

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Significance of a terminal R wave in Lead V_1 of the electrocardiogram

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A high amplitude terminal R wave associated with a broadened QRS complex in Lead V_1 is generally accepted as an ECG sign of a complete block *in the right bundle branch, while a terminal* r wave of low amplitude has turned out to be an ambiguous ECG pattern In most electrocardiographic textbooks a terminal r wave of low amplitude in Lead V_1 together with a prominent S wave in Leads V_5 and V_6, and the QRS duration from 0 09 sec to 0 11 sec are defined to indicate an *incomplete right bundle branch block* (ICRBBB)[4, 14, 29]

Several mechanisms have been suggested to cause a terminal r wave of low amplitude in Lead V_1 Experimentally a partial conduction delay in the right bundle branch has been shown to cause an rSr′ pattern[19] On the other hand, according to *Moore and associates*[15] *this pattern can occur in* right ventricular hypertrophy where conduction in the right bundle branch is normal Furthermore, in *clinicopathological correlative studies* Lenégre found that the right bundle branch was histologically normal in 76 per cent of the 33 patients with an ICRBBB pattern and that 94 per cent of them had a hypertrophied right ventricle[11] Also several other authors have suggested that the terminal r wave in Lead V_1 may be associated with right ventricular hypertrophy[2, 5, 10, 15, 17, 18, 27, 9] It may also develop in connexion with a myocardial infarction or left ventricular hypertrophy[1, 6, 7, 14, 16, 0] *The clinical significance of the terminal r wave in* Lead V_1 and its relationship to various cardiopulmonary combinations has not been fully evaluated In the *present study we have analyzed the occurrence of* the terminal r wave in Lead V_1 in healthy children and young adults as well as in middle aged and elderly patients with or without autopsy evidence of a cardiopulmonary disease

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Material and methods

The series is composed of the following groups

Group I 104 healthy children aged 3 to 14 years The mean age 8 5 years

Group II 207 healthy students 107 men and 100 women aged 20 to 30 years The mean age 24 3 years

Group III 171 hospital patients 62 men and 109 women aged 30 to 85 years who died with no autopsy evidence of a pulmonary or cardiac *disease The mean age 55 5 years*

Group IV 1,078 hospital patients 677 men and 401 women aged 30 to 92 years with a pulmonary and/or cardiac *disease verified at autopsy* The mean age 63 4 years

Characteristics of Groups III and IV have been described in a previous paper[2]

Electrocardiogram The ECGs were recorded with standard direct writing instruments One was a heated stylus recording instrument *with a frequency response* of 0 to 150 Hz (Cardiopan 3*) and the other an ink-jet recorder with a frequency response of 0 to 700 Hz (Olli 326†) *Cases with a complete right or* left bundle branch

*Liechti AG Bern Switzerland

†Olli Medical Electronics Helsinki Finland

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block as well as those with a WPW syndrome or idioventricular rhythm were excluded from the study

A terminal r wave in Lead V_1 was defined as follows the positive height more than 1 mm but less than 6 mm when the succeeding ST segment was used as a reference line The terminal r wave had to appear in every QRS complex of Lead V_1 The cases were divided into three types (Fig 1)

Type A The terminal r wave lower than the initial one in the same complex

Type B The terminal r wave higher than the initial one

Type C Cases with a Qr pattern in Lead V

An initial r wave was considered not to be present if it was lower than 0 25 mm Cases with the R/S equal to or greater than 1 in Lead V as well as those with an r′ wave followed by a terminal s wave (rsr′s) were excluded The ECG criteria of right ventricular hypertrophy (RVH) defined by Roman and colleagues [4] were used

Autopsy data Autopsy data on the hospital patients were based on routine autopsy protocols In postmortem examination enlargement of the heart right and left ventricular hypertrophy and signs of valvular or congenital heart disease were noted Five mm and 15 mm were determined as maximum thicknesses for the normal right and left ventricular walls Macroscopical evidence of significant pulmonary disease and the size and location of the myocardial infarction were recorded When necessary samples from the pulmonary or myocardial lesions were taken for microscopy

Results

A terminal r wave in Lead V in relation to age The occurrence of a terminal r wave of type A in Lead V decreased with age in healthy children healthy young adults and middle aged and elderly subjects without autopsy evidence of a cardiopulmonary disease (Table I) The QRS duration in children was from 0 06 sec to 0 07 sec and in healthy adults from 0 09 sec to 0 11 sec

A terminal r wave in Lead V in relation to a cardiopulmonary disease A terminal r wave in Lead V was found in 5 9 per cent (5 3 per cent in men and 7 0 per cent in women) of the middle aged and elderly patients in whom the autopsy revealed a significant pulmonary and/or cardiac disease (Table I)



Fig 1 Schematic presentation of type A B and C deformities of the QRS complex in Lead V

QRS deformities of types B and C were found only in patients with a cardiopulmonary disease while type A occurred in patients with or without autopsy evidence of cardiopulmonary disease In middle aged and elderly patients the prevalence of the A type deformity was the same (0 6 per cent) whether a cardiopulmonary disease was present or not No sex difference was found

The terminal r wave in Lead V_1 was found in 8 3 per cent of patients with right ventricular over load in 2 9 per cent of patients with left ventricular disease but no right ventricular overload and in 5 1 per cent of patients with both ventricles diseased (Table II) In 42 per cent of cases with a terminal r wave in Lead V_1 the free wall of the right ventricle was hypertrophied (Table II) This was the case in 30 per cent of cases with the B type and in 57 per cent of those with the C type deformity In not one case of the A type deformity was the right ventricle hypertrophied On the other hand the autopsy revealed a hypertrophied right ventricle in only 15 per cent of the middle aged and elderly patients with a cardiopulmonary disease in whose ECG no terminal r wave in Lead V_1 could be observed The highest frequency (10 per cent) of the terminal r wave in Lead V_1 was found in pulmonary patients with no myocardial infarction (Table II) The QRS duration in pulmonary patients with a terminal r wave was from 0 07 sec to 0 11 sec In half of them the autopsy revealed a hypertrophied right ventricle (Table II) In five cases of type B and in nine cases of type C the terminal r wave was the only ECG sign indicating right ventricular hypertrophy

There were seven cases with a terminal r wave where a myocardial infarction but no right ventricular disease was found In two cases the infarct was on the anterior and in one case on the posterior wall of the left ventricle Four patients had a combined anteroposterior myocardial infarction In four of the seven patients the

Table I Occurrence of a terminal r wave in Lead V_1

Series studied	Total number of cases		Number of cases with a terminal r wave in Lead V_1							
			Type A terminal r wave lower than the initial one		Type B terminal r wave higher than the initial one		Type C Qr type		Total	
	M	F	M	F	M	F	M	F	Number of cases	Per cent
Group I Healthy children	61	43	1	2	–	–	–	–	3	2 9
Group II Healthy young adults	107	100	1	2	–	–	–	–	3	1 4
Group III Autopsy cases with no evidence of cardiopulmonary disease	62	109	1	–	–	–	–	–	1	0 6
Group IV Cases with autopsy evidence of cardiopulmonary disease	677	401	4	2	12	11	20	15	64	5 9

duration of the QRS was 0 12 sec or 0 13 sec but the shape of the QRS complex did not indicate a complete right nor complete left bundle branch block All of these four cases had an infarction on the anterior wall of the left ventricle The material also included six patients with the terminal r wave in Lead V_1 associated with left ventricular hypertrophy but no myocardial infarction (three cases of aortic valvular stenosis three cases of cardiomyopathy) The free wall of the right ventricle was within normal limits in these cases, and the QRS duration was from 0 09 sec to 0 11 sec

Discussion

Two types of deformities rsr and rsr s in the QRS complex in Lead V_1 can occur They both have generally been linked with ICRBBB In the first type the terminal QRS forces are directed forwards and in the latter backwards According to Guller and associates[8] the backward directed terminal QRS forces are found in healthy children while the former type is associated with right ventricular hypertrophy The rsr s type also seemed to show greater positional and respirational changes[3] and has frequently (49 per cent) been found in healthy athletes who failed to show the rsr pattern[1] As these two types thus have different characteristics we limited the study only to the rsr deformity in Lead V_1

A terminal r wave in Lead V_1 has been found in up to 5 per cent of the ECGs of healthy children[4, 10] while it was an uncommon (0 2 per cent) finding in healthy adults[9] In the present study the occurrence seemed to decline with age 2 9 per cent in children, 1 4 per cent in young adults 0 6 per cent in middle aged and elderly subjects with no cardiopulmonary disease There are only a few studies where the terminal r waves in Lead V_1 are divided in different groups on the basis of comparison with the height of the initial r wave of the same complex[27, 28] In a Finnish population study on subjects aged 30 to 59 years the A type pattern as defined in this study was found in 2 9 per cent of men and 1 5 per cent of women and the B type pattern was found in 0 8 per cent of men and 0 6 per cent of women

The findings of the present study show that the A type deformity appears in the same frequency in healthy subjects as in subjects suffering from a cardiopulmonary disease and that type A is not associated with RVH On the other hand B and C type deformities did not occur in this study in subjects without evidence of a cardiopulmonary disease Our findings show further that the occurrence of the terminal r wave of type B or C in Lead V_1 is frequently involved with right ventricular hypertrophy Thus we can rightly presume that the terminal r wave higher than the initial one in middle aged and elderly subjects is an ECG sign pointing to a pathological state while an r wave lower than the initial one seems to be an innocent ECG finding Although we have not made histological studies of the right bundle branch we agree with Massing and James[17] and with Moore and colleagues[1] and regard it as

Table II Occurrence of the different types of terminal positivity in Lead V_1 in 1 078 subjects with autopsy evidence of significant pulmonary and/or left ventricular disease

Autopsy findings	Total number of cases		Number of cases with a terminal r wave in Lead V							
			Type A terminal r wave lower than the initial one		Type B terminal r wave higher than the initial one		Type C Qr type		Total	
	No	(RVH)	No	(RVH)	No	(RVH)	No	(RVH)	Number of cases	(RVH) %
Pulmonary disease without a myocardial infarction or valvular heart disease	311	(68)	2	(–)	11	(3)	17	(13)	30	(16)
Pulmonary disease with a myocardial infarction	123	(17)	1	(–)	1	(–)	1	(1)	3	(1)
Pulmonary thromboembolism without a myocardial infarction or valvular heart disease	165	(°6)	–	(–)	4	(2)	7	(3)	11	(5)
Pulmonary thromboembolism with a myocardial infarction	69	(13)	1	(–)	1	(–)	3	(1)	5	(1)
Valvular heart disease†	93	(21)	–	(–)	°	(–)	3	(1)	5	(1)
Congenital heart disease	5	(2)	–	(–)	–	(–)	–	(–)	–	(–)
A myocardial infarction but no pulmonary disease	1 8	(°3)	1	(–)	°	(°)	4	(1)	7	(3)
Coronary artherosclerosis but no myocardial infarction	4°	(–)	–	(–)	–	(–)	–	(–)	–	(–)
Left ventricular hypertrophy and cardiomyopathy	9_	(10)	1	(–)	2	(–)	–	(–)	3	(–)
Total	10 8	(180)	6	(–)	°3	(7)	35	(°0)	64	(°7)

Figures in the parentheses indicate the number of cases with RVH found at autopsy
†5? patients in this group had an additional pulmonary disease

misleading and incorrect to consider all cases with a terminal r wave in Lead V indicative of only ICRBBB

A terminal r wave in Lead V of type B or C sometimes occurs in pulmonary patients without evidence of a hypertrophied free wall of the right ventricle In these cases the hypertrophied outflow tract of the right ventricle may be the origin of the r patterns As expected right ventricular hypertrophy appears more frequently in patients with a C than with a B type deformity Type C is a final state of right ventricular overload and develops when the initial r wave disappears secondary to the rotation of the heart

A terminal r wave in Lead V was also found in some patients with left ventricular but no right ventricular disease It appeared in cases of an anterior myocardial infarction involved with a peri infarction block [20] and in some cases of strictly posterior myocardial infarctions [*] In the presence of a peri infarction block the QRS duration may be prolonged On the other hand in cases of left anterior hemiblock the terminal r waves tend to appear if the right precordial leads are recorded higher than usual [25]

It is concluded that the height of the terminal r wave in Lead V in subjects over 30 years of age has clinical significance if it is higher than the initial r wave in the same complex It is frequently associated with right ventricular overloading disease like right ventricular hypertrophy and sometimes with left ventricular disease A terminal r wave in Lead V_1 lower than the initial one tends to be an innocent finding

Summary

A terminal r wave in Lead V lower than 0 6 mV was studied in the ECGs of four groups (1) 104 healthy children (2) 207 healthy young adults (3) 171 patients with no autopsy evidence of a cardiopulmonary disease and (4) 1 078 autopsy patients with a cardiopulmonary disease Cases with a complete right bundle branch block were excluded A terminal r wave occurred in 2 9

per cent of healthy children, 1 4 per cent of healthy young adults 0 6 per cent of patients without and in 5 9 per cent of patients with autopsy evidence of a cardiopulmonary disease

The occurrence of a terminal r wave was most common in pulmonary patients (10 per cent) But it was also found in patients with an anterior or a posterior myocardial infarction and in some cases of left ventricular hypertrophy

In the autopsy series RVH occurred in 57 per cent of patients with a Qr pattern, in 30 per cent of patients with a terminal r wave higher than the initial one, and in none of the patients with a terminal r wave lower than the initial one

It is concluded that the height of the terminal r wave has clinical significance A terminal r wave higher than the initial one in Lead V_1 is associated with a cardiopulmonary disease in subjects over 30 years of age while an r wave lower than the initial one seems to be an innocent finding

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Evaluation of the heart rate response to the Valsalva maneuver

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High work load stress testing is widely used for the detection of subjects at high risk for coronary attacks Recently there has been increased interest in non exercise stresses such as the Valsalva maneuver which challenge the reflex control of the circulation and which may be monitored non invasively In the Valsalva maneuver the subject ordinarily holds a predetermined airway pressure (e g 40 mm Hg) for a brief period such as 15 to 30 seconds Intrathoracic and intraabdominal pressure rise aortic flow and pressure decrease and baroreflexes are triggered Throughout the straining release and recovery segments of the maneuver the blood pressure (BP) and the heart rate (HR) exhibit well defined changes in normal healthy subjects Characteristically HR is inversely related to the blood pressure events during the maneuver but patients with advanced coronary heart disease (CHD) exhibit much more sluggish responses to the Valsalva as reported by Elisberg[1] and ourselves One of our recent studies indicates that in normal subjects age importantly influences the HR response to the Valsalva maneuver

Because of the increasing evidence that HR may be a representative measure of the autonomic response to the Valsalva maneuver[3] we have in the present report analyzed the effect of age posture and CHD on the Valsalva maneuver and have derived a heart rate index that may be used to assess such a response and to identify abnormal Valsalva responses

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Procedure and methods

This report is based on data obtained over a five year period on five groups of normal white male subjects and two groups of white male coronary heart disease patients subjected to a series of stress tests Subjects with no evidence or history of cardiovascular disease who were free of hypertension hyperglycemia diabetes or any other obvious systemic disease and who had a negative physical exam and negative chest x ray prior to stress testing were classified as normals Those with typical history ECG and symptoms consistent with CHD were classified as cardiac patients In the 42 to 53 year old group of 11 CHD patients 10 had angina and a positive exercise treadmill stress test and seven of these had advanced coronary disease confirmed by cardiac catheterization and angiography The 50- to 64 year old cardiac group was composed of 11 ambulatory CHD patients all with a history of angina and (two or three vessel) coronary artery disease as documented by coronary angiography

In all patients medication was stopped for a sufficient period prior to testing to insure non interference with functional response to the tests Each subject performed the Valsalva maneuver by expiring forcefully and maintaining a constant airway pressure of 40 mm Hg for 15 seconds (open glottis) In some of the groups the maneuver was carried out in the supine sitting and standing positions Two groups (II and III Table I) of subjects performed only the Valsalva maneuver in the remaining the Valsalva maneuver was one of a series of five non invasive tests

Heart rate was monitored from bipolar ECG chest leads the ECG and airway pressure were recorded simultaneously on a Grass Polygraph (Model 5P4) Fig 1 shows a typical instantaneous HR response of a 39 year old normal male before

Table I Heart rate during the 15 second Valsalva maneuver

Group	*Age*	*Posture*		*Control*	*Phase 1*	*Phase 2*	*Phase-3*	*Phase-4*
Normal	Mean = 23 5	Supine	Mean	74	63	92	103	59
Group I	S D = 2 9		SEM	2	2	5	3	2
19 26								
Years	N = 11	Standing	Mean	92	73	118	125	65
			SEM	2	3	4	4	3
Normal	Mean = 23 1	Supine	Mean	66	72	103	109	57
Group II	S D = 1 9		SEM	3	4	7	6	2
20-29								
Years	N = 10	Sitting	Mean	74	73	110	114	53
			SEM	4	5	8	8	2
		Standing	Mean	82	85	118	121	58
			SEM	4	6	7	8	4
Normal	Mean = 34 3	Supine	Mean	65	75	95	102	55
Group III	S D = 3 2		SEM	3	5	8	8	2
30 39								
Years	N = 9	Sitting	Mean	66	64	86	96	53
			SEM	4	4	8	7	2
		Standing	Mean	72	67	101	108	53
			SEM	5	4	8	8	6
Normal	Mean = 45 1	Sitting	Mean	62	68	88	90	59
Group IV	S D = 2 9		SEM	2	3	4	5	2
40 49								
Years	N = 17 (30)*							
Normal	Mean = 51 4	Supine	Mean	57	66	86	91	57
Group V	S D = 3 1		SEM	2	3	4	3	2
47 56								
Years	N = 10	Sitting	Mean	60	63	87	94	57
			SEM	2	2	2	2	2
		Standing	Mean	69	73	97	101	64
			SEM	2	3	2	2	4
Cardiac	Mean = 49 2	Sitting	Mean	68	75	92	91	69
Group I	S D = 4 5		SEM	3	4	5	5	3
42 53								
Years	N = 11 (18)*							
Cardiac	Mean = 56 8	Supine	Mean	72	78	94	97	73
Group II	S D = 4 1		SEM	3	3	3	4	4
50 64								
Years	N = 10	Sitting	Mean	77	78	94	97	77
			SEM	4	3	3	4	4
		Standing	Mean	84	86	105	108	81
			SEM	4	3	3	3	4

In these studies most of the subjects were given two independent trials of the stress battery Therefore the total number of trials is given in parenthesis following the number of subjects

during and after performing the Valsalva maneuver in the supine position The HR response was scored by determining (1) the mean control HR (2) the Phase 1 HR as the lowest rate immediately after straining is initiated (3) the Phase 2 HR as the fastest rate at the end of the straining period (4) the Phase 3 HR as the maximum rate just following release and (5) the Phase 4 HR as the slowest rate observed during the ensuing bradycardia

Statistical analysis of the data was performed using the appropriate analysis of variance to assess the main effects of age posture Valsalva phases, CHD and corresponding interactions on

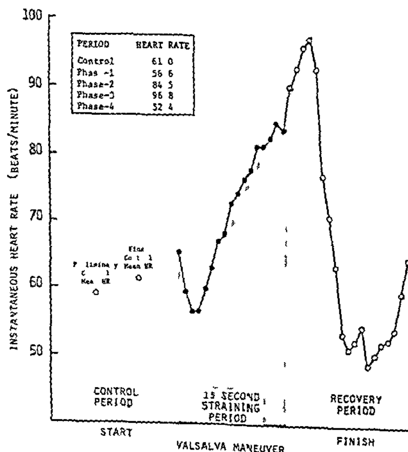


Fig 1 Instantaneous heart rate during the Valsalva maneuver for a 39-year old normal male *in* the supine position Control means are average rates for " seconds and the control period is the two minutes preceding the test The recovery period is about 20 seconds in duration

the heart response Discriminate analysis was used to help identify variables capable of distinguishing normal from CHD like responses Multiple linear regression was employed to describe the characteristic average HR response of normals in terms of additive combinations of other easily identified variables

Results

The effects of age posture and CHD on heart rate The mean control and phase HR s during the Valsalva maneuver are shown in Table I for each of the five normal and two CHD study groups Age and posture effects were assessed by using analysis of variance on the heart rates of the 20- to 29 year old normal Group II and the 50 to 59 year old normal Group V Fig 2 displays the group average HR s for the Valsalva maneuver in each of three body positions in normal subjects Results of the analysis of variance showed that significant factors were age ($P < 025$) phases of the Valsalva maneuver ($P < 001$) posture ($P < 001$) and phase by age group interaction ($P < 01$) The effect of age was evidenced by generally lower heart rates for the 47 to 56 year old normals The posture effect was shown by the elevated HR s in the standing position with respect to supine and sitting positions ($p < 001$) The difference between heart rates in the supine and sitting position are minimal for corresponding phases ($1 < P < 2$) As expected the phases of the Valsalva maneuver elicited the most pronounced effect illustrating the progressive rise from control or Phase 1 to Phase 2 and 3 and the sharp slowdown in Phase 4 The significant phase by age group interaction results mainly from greater control to peak and greater peak to Phase 4 values in young normals

To test for the CHD effect analysis of variance was applied to the HR s of the 47 to 56 year-old normal group and the 50 to 64 year old cardiac

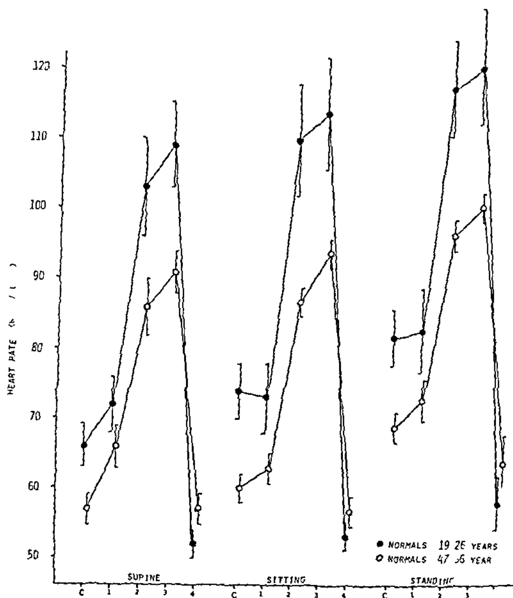


Fig 2 Control and Valsalva phase heart rates in supine, sitting and standing positions in two groups of normal men (C = control and 1 2 3 and 4 denote the phase HR s mean ± SEM)

group Patterns of HR means for these two groups are displayed in Fig 3 Significant factors were CHD ($P < 005$), phases of the Valsalva maneuver ($P < 001$), and the phases by (normal cardiac) interaction The interaction effect is due to the greater rate increases (control and Phase 1 to Phase 2 and 3) and more pronounced rate decreases (Phase 2 and 3 to Phase 4) in normals than cardiac patients

From control to Phase 1 of the Valsalva maneuver a reflex HR slowing should be observed [3] We observed this slowing in 72 per cent of the trials of young normals (Group I and II) in 48 per cent of the trials of thirty year old normals (Group III), in 35 per cent of the forty year old normal trials (Group IV) and in 23 per cent of the fifty year old normal trials (Group V) However only 19 per cent of the cardiac trials exhibited a control to Phase 1 decrease in heart rate

Elisberg[1] reported that all of his normal subjects had Phase 4 HR s below control HR levels but that this occurred in only 4 5 per cent of the advanced cardiac patients In our study Phase 4 HR was less than the control HR in about 75 per cent of the normals (particularly the 19 to 26 year olds where it occurred in 90 per cent of cases) and also in 47 per cent of the cardiac patients

Discrimination of cardiac from normal responses As is evident from the analysis of mean HR responses the two cardiac patient groups exhibited HR patterns significantly different from the normals during the Valsalva maneuver However, to have clinical value the altered pattern of HR s in CHD should indicate discriminatory statistics that allow the identification of

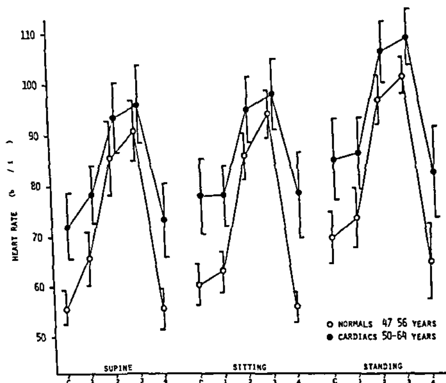


Fig 3 Control and Valsalva phase heart rates in supine sitting and standing positions in normal men and cardiac patients (C = control and 1,2 3 and 4 denote the phase HR s mean ± SEM)

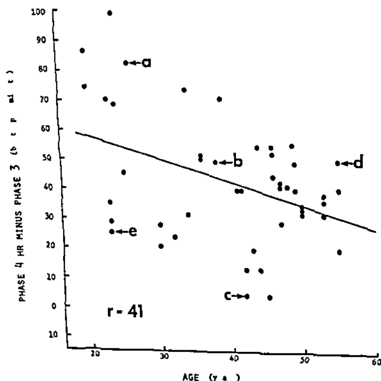


Fig 4 Relation of age and Phase 3 to Phase 4 heart rate change for normal subjects Letters *a* to *e* identify five normal subjects in Table II

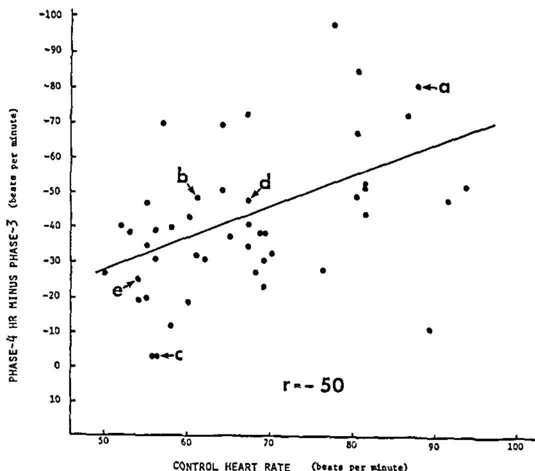


Fig 5 Relation of control heart rate and Phase 3 to Phase 4 heart rate change for normal subjects

atypical heart rate responses The control to Phase 4 value Δ(C 4), suggested by Elisberg was quite reliable in discriminating advanced heart disease but in an additional group of clinically less advanced heart disease, only five of the 30 patients responded with an atypical HR change[3] Among our cardiac patients only 53 per cent would be classified in the heart disease category by Δ(C,4) and moreover about 25 per cent of our normals would fall into the heart disease group on this basis

In an effort to identify either a single HR or combination of HR s from the pattern that can be used to distinguish the normal from the cardiac response, we applied linear discriminant analysis to the HR s of 11 pairs of age matched normals and cardiac patients The results indicated that Δ(C,4) was not a satisfactory measure and the best single linear discriminator was the Phase 3 to Phase 4 change in heart rate Δ(3 4) Addition of any other single phase HR or combination of the phase heart rates did not significantly improve discrimination over the Δ(3 4) This was also the case when log transformed HR s were subjected to the same analysis procedure

Scoring the heart rate response Using all the HR s from Valsalva maneuvers in normal subjects performed in the sitting position we found the Δ(3,4) was significantly correlated with age (A), with the control HR (C) and with the Phase 3 heart rate (P_3) These three individual relationships are illustrated in Figs 4 5 and 6 respectively Moreover, Δ(3,4) can also be explained simultaneously in terms of (1) A C and P_3, or (2) A and P_3 by the multiple regression equations

$$\Delta(3\ 4) = 19\ 95 + 368A + 348C - 1\ 008P_3 \quad (1)$$

$$\Delta(3\ 4) = 35\ 80 + 285A - 906P_3 \quad (2)$$

Multiple regression analysis shows that one standard deviation unit that represents the scatter of normal responses about the average expected response is 5 75 (beats per minute) for (1) and 6 45 (beats per minute) for (2)

On this basis it is possible to score an individual s HR response to the Valsalva test by using the observed Phase 3 to Phase 4 change (denoted $\Delta_0(3\ 4)$) A, C and P_3 If responses of healthy subjects follow a normal distribution, then standardized Valsalva scores (VS) would be

$$VS(A\ C\ P_3) = \frac{\Delta_0(3\ 4) - (19\ 95 + 368A + 384C - 1\ 008P_3)}{5\ 75}$$

$$VS(A\ P_3) = \frac{\Delta_0(3\ 4) - (35\ 8 + 285A - 906P_3)}{6\ 45}$$

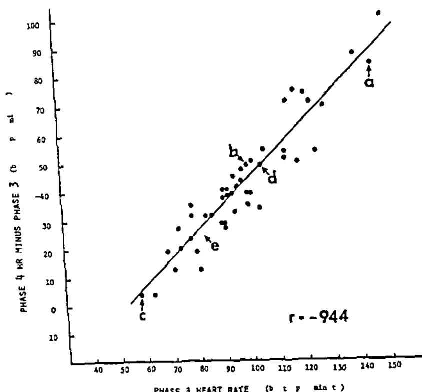


Fig 6 Relation of Phase 3 heart rate and Phase 3 to Phase 4 heart rate change for normal subjects.

Both Valsalva scores were constructed so that for normal healthy individuals the average score would be zero with about 95 per cent of the scores falling in the −2 to +2 range Our 45 normals had an average VS(A C P_3) equal to −002 (SD = 0 98) and had an average VS(A P) of 0 00 (SD = 78)

Diminished bradycardic responses typical of circulatory disease would have large positive Valsalva scores The mean VS(A C P) of our cardiacs was 1 53 (SD = 1 84) and the corresponding mean VS(A P) was 1 99 (SD = 1 92) Using VS(A C P_3) 18 of 21 cardiac patients in our series had positive Valsalva scores Of the 18 ten scores ranged from 1 668 to 5 23 and six of these belong to the older cardiac group Our cardiacs exhibited more dispersion in derived Valsalva scores probably because these subjects represent different stages of CHD

Those normals and cardiac patients who were measured on two independent Valsalva tests were used to investigate the repeatability of Valsalva scores The 40- to 49 year-old normals showed moderately high and statistically significant intraclass correlation coefficients of 0 678 for VS(A C P_3) and 0 675 for VS(A C P) ($P < 01$) The 42 to 53 year old cardiac group yielded intraclass correlation coefficients of 0 804 for VS(A C P_3) and 0 842 for VS(A C P_3) ($P < 01$) Differences in test one and test two average VS s were not statistically significant for either group Cardiac patients showed high intraclass correlations because of a wider range of cardiac scores

Discussion

In most groups there were only minor differences between HR s in the supine and sitting positions The general effect of the upright posture was mainly to elevate both control and phase heart rates however this effect was complicated by the tendency of some subjects (usually those in better physical condition) to show lesser heart rate elevations during standing This was most evident in the increased dispersion of Phase 4 heart rates during standing for the normal group (II III and V in Table I) These results suggest that a more valid comparative assessment of the Valsalva response can be made when performed in the supine or sitting position

While age has not received much attention in prior Valsalva studies[2,3,7,9,10] it is clearly an important factor in determining the response in normal males [5] Our analysis showed that in older individuals there is a general tendency for

Table II Illustration of Valsalva scores for five normal subjects and three cardiac patients

	Age (years)	Control heart rate (per min)	Phase 3 heart rate (per min)	Observed $\Delta_o(3\ 4)$ (per min)	Predicted $\Delta(3\ 4)$ (per min)	VS (A C P_3)	Predicted $\Delta(3\ 4)$ (per min)	VS (A P_3)
(a)	26	87	146	−82	−87 4	94	−89 1	1 11
(b)	38	61	100	−48	−45 7	− 40	−44 0	− 62
Normal (c)	42	56	58	− 3	− 3 6	10	− 4 8	28
(d)	55	67	105	−48	−42 4	− 98	−43 7	− 66
(e)	23	54	82	−25	−35 5	1 82	−31 9	1 08
	40	65	74	−17	−17 1	04	−19 9	43
Cardiac	48	71	86	+ 2	−24 4	4 58	−28 4	4 70
	55	85	96	−12	−27 3	2 61	−35 9	3 66

control HR's to decrease (Table I) but the predominant age effect is a decline in the degree of HR change between phases, particularly Δ(3,4) Multiple regression analysis indicated that with other factors held constant there was a 3 to 4 beat per minute reduction in heart rate response (Δ(3 4)) for each additional 10 years of age This strongly implies that Valsalva responses should be judged relative to responses of healthy subjects of equivalent age Other Valsalva studies report higher control HR s than our normals[3, 10], this might be due to inclusion of younger subjects or to testing conditions less suited to quiet surroundings and baseline conditions

Our CHD patients had higher resting HR's and significantly lesser HR changes during the Valsalva These differences were more pronounced in the 50 to 64 year age group than in the 42 to 53 year group[5] Discriminate analysis indicated that the Phase 3 to Phase 4 change Δ(3 4) is the preferred discriminator between normals and cardiacs The Δ(3 4) difference is not seriously influenced by factors that elevate the control HR From Phase 3 to Phase 4 the HR responds almost entirely to the dramatic changes in blood pressure which activate the autonomic circulatory control mechanisms The autonomic response in turn is influenced by the subject's health, age and posture Since our studies thus far have been confined to white male subjects we cannot at present evaluate the possible effect of sex or race

The proposed Valsalva score will identify responses that deviate from the expected average normal for a given age, control HR, and Phase 3 heart rate An abnormal response is indicated by a score of +2 or larger With this method few normals will have large scores (high specificity) While not all CHD subjects will have large scores a high score would theoretically suggest possible cardiac dysfunction Valsalva scores from five normal subjects and three CHD patients are given in Table II Normal individual e' has a suspiciously high VS(A,C,P_3) but VS(A,P_3) which does not use the control HR is more indicative of a normal score Of the three cardiacs in Table II, two had high scores and one had a quite normal score

A high Valsalva score might be associated with circulatory abnormalities other than CHD Using data from a Valsalva like maneuver administered to three groups in a study by Goldberg and colleagues[10] calculations indicate that three normals have VS(A,C P_3) s of 0 12, 0 47, and 1 83 the last is suspiciously high for a 34 year old Three patients with mild mitral stenosis had scores of 2 53, 27, and 2 29 Two of these scores indicate abnormal heart rate responses to the Valsalva test Finally a group of four patients with severe mitral stenosis (ages 22 23 33, and 39 years) yielded extremely high VS(A,C P_3) s of 5 52 6 33, 6 59, and 5 70

Abnormal Valsalva responses may also be associated with diabetic autonomic neuropathy which may affect autonomic control of the heart In a previous study of the Valsalva response in 13 patients with this diabetic complication it was reported that reflex bradycardia was absent in seven and small in the remainder and even in the two patients with normal blood pressure overshoot, almost no heart slowing resulted[11] The HR responses in these patients would result in large scores using our method of analysis In another study of 21 diabetic outpatients (mean age 44 9 years range 11 to 71 years) only seven of 17 successful patient trials showed normal Valsalva bradycardia[12]

The HR changes during the Valsalva maneuver

are due to autonomic reflexes as evidenced by the fact that these changes may be minimized or eliminated by autonomic blockage[2] The mechanisms underlying diminution of the heart rate response to the Valsalva with advanced age and heart disease are not certain but may be related to altered baroreceptor sensitivity *per se*[3] Because coronary artery disease is likely to be accompanied by general systemic arteriosclerosis this factor may contribute to reduce baroreflex sensitivity and thus result in a lesser HR effect Alternatively there may be diminished blood pressure changes in the Valsalva maneuver associated with hemodynamic mechanical factors such as decreased venous compliance or increased central blood volume[3] either of these would diminish the usual restrictive effect of the Valsalva on cardiac filling and thus reduce the blood pressure changes presented to the baroreceptors

It seems evident that two general mechanisms—those associated with hemodynamic factors or those associated with baroreflex responsiveness—may contribute to an abnormal response to the standard Valsalva test Such altered responses may occur normally with advancing age or in certain cardiac or neuropathic conditions It is important however to distinguish between the normal and the pathological Therefore we believe that a non invasive monitoring of the heart rate response to the Valsalva maneuver and the characterization of the response in terms of age posture and Phase 3 HR may be a clinically useful technique for the early detection of heart disease

Summary

A study has been made of the heart rate (HR) response to the Valsalva maneuver in five different groups of normal white males and two groups of male coronary heart disease (CHD) patients using non invasive methods By means of the analysis of variance the effects of age posture Valsalva phase and CHD on the HR response were assessed Both age and CHD were factors that reduce the HR response Further analysis indicated that the HR change from Phase 3 to Phase 4 in the Valsalva was the preferred discriminator between normals and cardiac patients We have derived a Valsalva score that can be used to identify HR changes that deviate from the expected average normal response for a given age control HR and Phase 3 HR HR assessment of the Valsalva maneuver is a simple safe non invasive test An abnormal response suggests altered functioning of hemodynamic or autonomic cardiovascular mechanisms governing HR control

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Involvement of the cardiac conducting system in panarteritis nodosa

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Heart *involvement* is *common* in panarteritis nodosa and arteritis of the extra and intramural coronary arteries with aneurysmal dilatation and thrombosis, myocardial infarction, pericarditis and hypertensive cardiopathy are the most *frequently* reported cardiac lesions [1]

Although arrhythmias, mainly from impulse formation, have been described in panarteritis, the conducting system has not been extensively studied [2,3] This paper reports the histopathological findings in conducting tissues in three successive, unselected cases of panarteritis nodosa

Definition of terms and methods

The classical features of panarteritis, consisting of necrotizing angiitis of the middle small sized systemic arteries[4,5] were observed in all three cases According to Zeek[6] and Allarcon Segovia and Brown *true panarteritis nodosa should* be distinguished from other forms of necrotizing angiitis such as hypersensitivity angiitis and Wegener granulomatosis, in which the inflammatory process involves the arterioles and veins as well as vessels of the pulmonary vascular bed

The histopathological investigation of the conducting system was carried out by removing the sinoatrial node and the Tawarian system from the formalin fixed hearts and processing these tissues for histology The paraffin embedded blocks were sectioned in series retaining two sections every 20 which were stained with Haematoxylin Eosin and Elastic Van Gieson stains

Case 1

A 9 year old girl was admitted to the Pediatric Department of our University presenting with *fever, skin rash and cardiac murmur The blood* pressure, normal at first, increased significantly and reached values as high as 240/140 mm Hg The nephrotic syndrome was present Hepatitis B (Australia) antigen was found in the serum, the *plasma renin was increased The electrocardio*gram showed left ventricular overload and a Q wave in Lead aV_L (Fig 1) Systemic hypertension and renal insufficiency became more severe notwithstanding antihypertensive corticosteroid *and immunosuppressive therapy and the patient* died 3 months after admission from heart failure and uremia

Main postmortem findings were pulmonary edema bronchopneumonia left ventricular hy*pertrophy* (heart weight 280 grams) healed panarteritis of the coronary arteries with aneurysms and thrombosis coarsely nodular surface of the kidneys with old thromboses of the arcuate arteries and polyvisceral healed panarteritis which however spared the spleen and the lungs

Histology of the conduction system The SA node *and its main artery were free from lesions* The AV node was arranged around a central artery which showed severe fibrosis destruction of the tunicae elasticae and luminal occlusion from an old recanalized thrombus (Fig 2) The central fibrous body *showed several gaps* at the fusion point between the aortic and tricuspid rings *and the pars membranacea* septi was markedly underdeveloped The septal tricuspid

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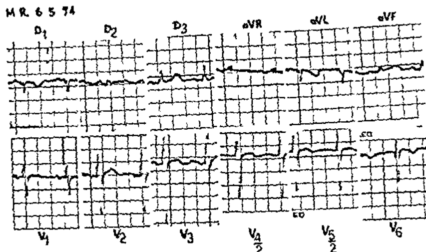


Fig 1 Case 1 The electrocardiogram recorded 5 days before death shows Q waves in D and aV$_L$ and biventricular hypertrophy

leaflet had a high insertion and the conal septal muscle extended posteriorly Due to the overdevelopment of the conal musculature the His bundle had an anterior intramyocardial course towards the left side and a small artery was present with aneurysmatic dilatation of the fibrotic wall (Fig 3) The bifurcation on the left side of the ventricular septum and the bundle branches were normal

Case 2

A 28 year old man was admitted presenting with transient amaurosis systemic arterial hypertension and signs of congestive heart failure Blood pressure was 210/140 mm Hg The electrocardiogram recorded left ventricular hypertrophy (Fig 4) Australia (Au) antigen was present in the serum The hypertension did not respond to therapy and the patient underwent two episodes of pulmonary edema Corticosteroids were administered Renal function deteriorated progressively After repeated attacks of abdominal angina the patient died suddenly

The main postmortem findings were pulmonary edema bilateral pleural effusion cardiomegaly with left ventricular hypertrophy recent cardiac infarction of the right auricle and crista terminalis coarsely nodular surface of the kidneys with obstructed intrarenal arteries recent multiple infarctions in the spleen kidneys pancreas and testes Healed polyvisceral panarteritis

Histology of the conduction system The SA node centered with the nodal artery suboccluded by a partially recanalized thrombus showed extensive coagulative necrosis involving the SA nodal approaches and the contiguous ordinary atrial myocardium (Fig 5) The AV node the His bundle and the bundle branches were normal (Fig 6) The proximal right bundle branch had an intramyocardial course The AV node artery was supplied by several arterioles

Case 3

A 39 year old man was admitted to the University Hospital for sudden bilateral amaurosis Blood pressure was 250/150 mm Hg Renal function texts revealed severe impairment The patient underwent recurring pulmonary edema Hypotensive therapy succeeded in reducing systemic pressure to about 170/90 mm Hg One year later the patient had attacks of abdominal angina He was readmitted to Hospital with blood pressure at 230/130 mm Hg The electrocardiogram was normal (Fig 7) Due to the worsening of abdominal conditions a laparotomy was performed and an infarction of the small intestine was detected and resected Histological observation of the surgical specimen revealed mesenteric arteritis with occlusive thrombosis Two days following surgery atrial arrhythmias were recorded on monitoring On the next day the patient died suddenly

The main postmortem findings were pulmo

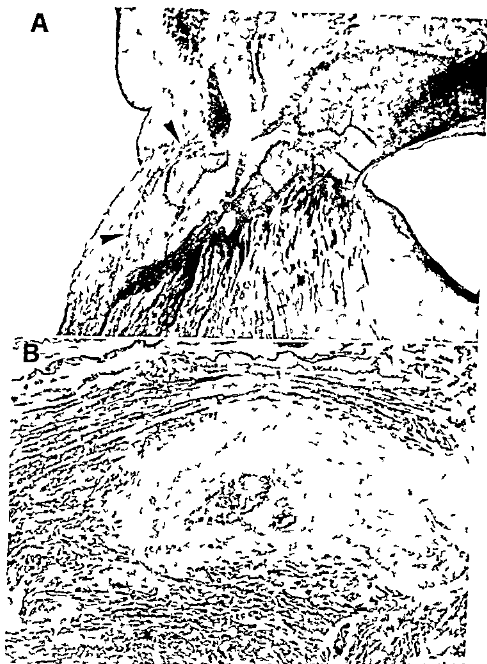


Fig 2 Case 1 *A* The AV node *(arrows)* (Elastic Van Gieson stain original magnification ×12) *B* The twin section shows bifurcation of the AV nodal artery with old thrombosis and healed panarteritis severe periarterial fibrosis and atrophy of the adjacent specific tissue (Hematoxylin and eosin stain original magnification ×60)

nary edema heart enlargement (470 grams) with left ventricular hypertrophy moderate athero sclerosis of the subepicardial coronary arteries multiple renal infarctions, acute panarteritis including aneurysmatic dilatations involving mainly the small coronary and renal arteries

Histology of the conduction system The SA nodal artery and its branches exhibited acute necrotizing angiitis with fibrinoid necrosis and leukocytic infiltration (Fig 8*a*) Aneurysmatic dilatation by rupture of the tunicae elasticae also was observed (Fig 8*b*) The infiltration of the arterial wall with inflammatory cells extended to the surrounding specific tissue involving also the SA nodal approaches The AV node was normal and two small arteries within it were free from lesions (Fig 9*a*) The His bundle bifurcation was astride the crest of the ventricular septum (Fig 9*b*), and the bundle branches were normal

Discussion

The three cases of panarteritis reported exhib ited significant lesions of the specialized conduc tion system of the heart due to either acute or healed angiitis of the nutrient arteries of the conducting system In Case 1 healed vasculitis of the AV nodal artery was associated with exten sive periarterial fibrosis and atrophy of the AV

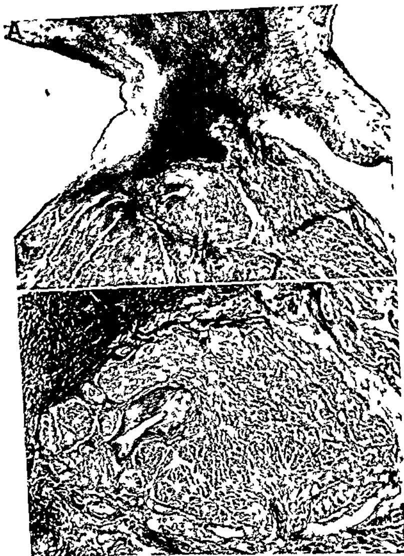


Fig 3 Case 1 *A* The distal tract of the common bundle below an underdeveloped membranous septum *B* its artery shows rupture of the tunicae elasticae and fibrotic dilatation (Elastic Van Gieson stain original magnifications A×19 B×48)

nodal specialized muscle In Case 2 arteritis of the SA nodal artery was complicated by a recent thrombosis associated with massive infarction of the SA nodal tissue and its atrial approaches Case 3 showed acute necrotizing angiitis of the SA nodal artery with fibrinoid necrosis aneurysmal dilatation of the vascular wall and phlogistic infiltration of the surrounding SA node specific tissue Hence the pathogenetic mechanisms for the conducting system lesions in panarteritis nodosa may be either ischaemic or inflammatory in nature from occlusion of the nutrient arteries or extension of the inflammation and fibrosis to the periarterial tissue respectively

James and Birk[2] have carried out a fundamental study of the conducting system in six cases of angiitis and were the first to emphasize that since the nutrient arteries of the SA and AV nodes were ideal in size to be involved in arteritis the periarterial layout of both nodes renders them highly vulnerable to these diseases In their series they describe two cases with true panarteritis nodosa one with acute inflammatory involvement of the SA nodal artery and the other with infarction of the SA node In both patients severe atrial dysrhythmias were recorded and one patient died suddenly

Syncopal seizures probably from AV block

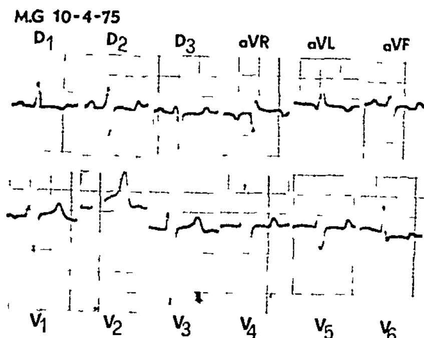


Fig 4 Case 2 Electrocardiogram left ventricular hypertrophy and prolongation of the QT segment

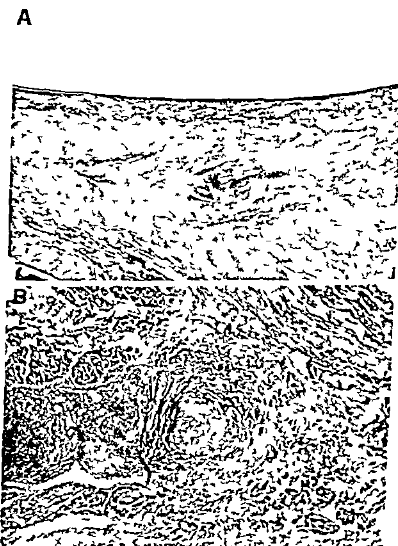


Fig 5 Case 2. A SA node with severe stenosis of the SA nodal artery (Elastic Van Gieson stain original magnification ×12) *B* An adjacent section of the SA node shows recent thrombotic occlusion of the nodal artery and coagulative necrosis of the specific tissue (Hematoxylin and eosin stain original magnification ×60)

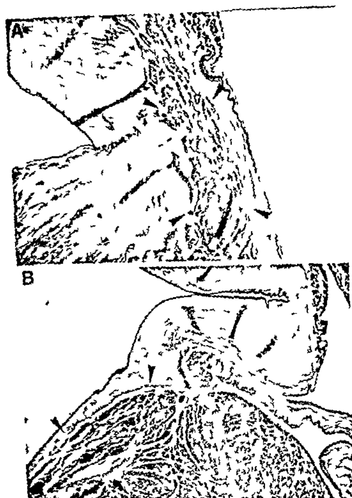


Fig 6 Case 3 The AV node *(A)* and the branching portion of the His bundle *(B)* are free from lesions *(arrows)* (Hematoxylin and eosin stain original magnification ×19)

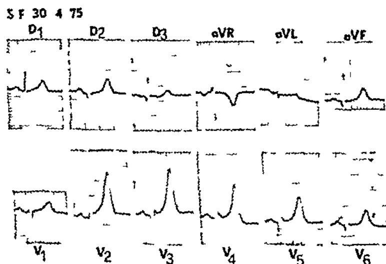


Fig 7 Case 3. The electrocardiogram without significant alterations

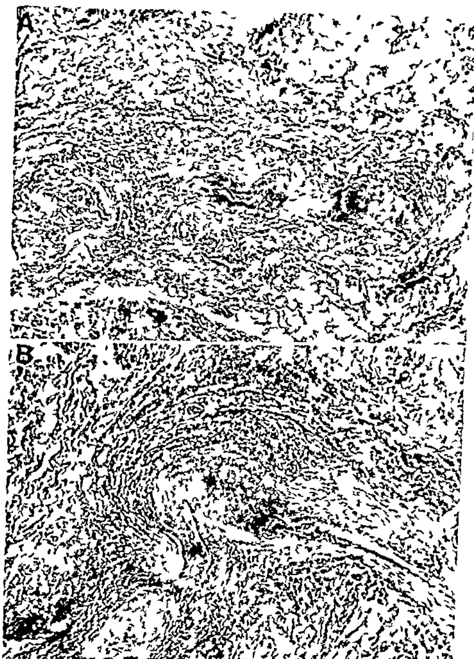


Fig 8 Case 3 *A* Acute necrotizing arteritis of the SA nodal artery with fibrinoid necrosis and leukocytic infiltration *B* aneurysmal dilatation and periarterial phlogistic infiltration of the specific nodal tissue (Hematoxylin and eosin stain original magnification ×60)

were further reported by Tang and Segal[7] in an infant with panarteritis nodosa on histological examination subocclusion of the AV nodal artery with periarterial fibrosis was observed as in Case 1 of our series

Our observations endorse the foregoing reports concerning the significant association of panarteritis with conducting system disease due to involvement of the nutrient arteries With regard to the apparent clinicopathological discrepancy in our first two patients who failed to show the expected electrocardiographic manifestations of damage to cardiac specialized tissue it is known that the early clinical signs of diseased sinoatrial and/or atrioventricular activation are at times very elusive It has been claimed that in apparently normal individuals the only evidence of Sick Sinus Syndrome often consists of brief and transient arrhythmias whose recognition may require cardiac monitoring over periods of 24 hours or more[8] Indeed only our third case underwent cardiac monitoring and happened to exhibit atrial dysrhythmias that had completely escaped recording by the standard surface electrocardiograms Sudden death in this case and in patient No 2 may also be tentatively explained by the

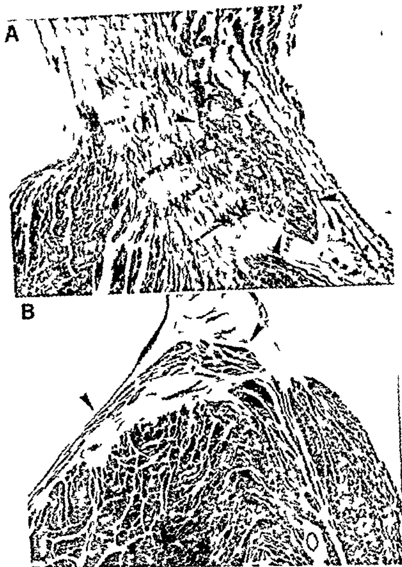


Fig 9 Case 3. A The distal AV node and B the branching portion of the His bundle free from lesions *(arrows)* (Hematoxylin and eosin stain original magnification ×19)

fatal outcome of a cardiac arrest and/or arrhythmic attack complicating SA or AV conduction impairments

Our cases of panarteritis nodosa were not selected on the basis of electrocardiographic evidence of arrhythmias In our opinion the postmortem finding of pathologic lesions of the specific cardiac tissue in all three hearts supports the view that panarteritis nodosa involves the conducting system often enough to represent on pathophysiological and clinical ground a major impending threat to the patients irrespective of existence of related rhythm disorders on occasional surface electrocardiograms and routine medical examinations Protracted cardiac monitoring and appropriate controls by catheter recording and stimulation techniques are highly recommended in these patients whenever possible for early detection and prevention of life threatening arrhythmias from altered impulse formations and conduction

Summary

Histopathological observations on the conduction system of the heart were carried out in three cases of panarteritis nodosa This specialized tissue was involved in each case secondary to ischemia and/or periarterial extension of the

inflammatory process affecting the nutrient arteries of the conducting system The high risk of disturbances in impulse formation and conduction in patients with panarteritis is emphasized as well as the need for appropriate clinical investigation (protracted cardiac monitoring and control by catheter recording and stimulation) in order to secure early detection and prevention of life threatening arrhythmias

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Vagal tone significance of electrophysiologic findings and clinical course in symptomatic sinus node dysfunction

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The role of vagal tone in symptomatic sinus node dysfunction is subject to much controversy [s] Some authors assume that massage of the carotid sinus in the presence of sick sinus syndrome (SSS) causes excessive slowing of the heart since it is thought that marked organic disease of the sinus node predisposes excessive responses to vagotonic maneuvers However relative unresponsiveness to atropine was found in SSS in a majority of cases studied by others [1 3] suggesting sinus node dysfunction independent of the carotid sinus reflex In a previous study we found no evidence of SSS in patients with hypersensitive carotid sinus reflex (HCSR) and we assumed that symptomatic sinus node dysfunction was caused by excessive response to vagal stimulation

The indication for pacer application in HCSR and SSS is often based on severe clinical symptomatology rather than on the specific test results A systematic evaluation of the literature regarding the course of HCSR and SSS is lacking and yet information of this sort could be useful for therapeutic considerations such as pacer application The present study was intended to (1) investigate vagal influence on HCSR and SSS (2) ascertain if the combination of HCSR + SSS found in the same patient might at least in part be based on an uniform physiologic concept (3) try to classify or correlate symptomatic severity of both syndromes and electrophysiologic findings as regards their clinical implication and (4) analyze the course of SSS by restudying a group of patients

Patients and methods

The population under study consisted of 186 symptomatic patients with complaints of dizziness syncope an inability to concentrate or a combination of these symptoms Forty patients were female 146 were male Their mean age was 58 3 ± 11 4 years Cerebrovascular disease acute myocardial ischemia aortic stenosis third degree AV block and subclavian steal syndrome were all excluded as possible causes for syncope and dizziness The patients were divided into four groups according to the results of electrophysiologic testing group I consisting of 103 patients with evidence of HCSR showed a maximum P P interval (P P vs R R $p > 0 05$) > 3 sec following carotid sinus pressure (CSP max) [3] Thirty three patients with a combination of both HCSR + SSS (CSRT max $\geqq 560$ msec CSP max $\geqq 3$ sec respectively) [2 3 t] made up group II Group III consisted of 30 patients with evidence of isolated SSS Group IV included 20 patients who according to complete testing showed no evidence of either HCSR or SSS Clinical data symptoms and ECG findings of the four groups are listed in Table I 16 3 ± 10 5 months after the initial investigation another 16 patients with SSS were restudied in order to analyze the natural course of this syndrome

Prior to study a complete medical history and physical examination chest x ray ECG as well as informed consent were obtained in all patients At the time of study all cardioactive medication

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Table I Clinical data of the 186 patients investigated

		Group I (HCSR)	Group II (HCSR + SSS)	Group III (SSS)	Group IV (Control)
Patients	No of cases	103	33	30	20
	Age (years mean)	59 9	60 6	55 3	57 3
	Female patients	15%	27%	46%	15%
	Male patients	85%	73%	54%	85%
Symptoms	Syncopes	14%	9%	18%	0
	Dizziness	25%	27%	36%	35%
	Syncop + dizziness	41%	45%	42%	0
	Others	20%	19%	4%	65%
	Total	100%	100%	100%	100%
Additional diseases	Congenital heart disease	2%	6%	11%	0
	Rheumatic heart disease	9%	3%	11%	10%
	Coronary heart disease	37%	42%	39%	34%
	Hypertension	36%	33%	14%	35%
	Chronic pulmonary disease	9%	3%	7%	18%
	Others	7%	13%	18%	3%
	Total	100%	100%	100%	100%
Routine ECG Findings	S A block (arrest)	15%	39%	63%	5%
	PAC s	6%	24%	43%	5%
	AF (intermitt)	21%	27%	25%	10%
	Atrial flutter (intermittent)	2%	15%	19%	0
	PAT (with block)	8%	21%	14%	0
	A V 1° block	14%	12%	10%	5%
	PVC s	18%	24%	26%	15%
	RBBB LBBB LAD	36%	27%	16%	28%

had been discontinued for an interval exceeding three drug half lives All patients were studied in the resting nonsedated, postabsorptive state Two transvenous catheter electrodes were positioned high on the lateral wall of the right atrium One was used for bipolar stimulation of the atrium the other for recording atrial electrograms which were registered by a multichannel ink writing system simultaneously with surface ECG leads or by using His bundle recordings [36] In only a few cases were multichannel surface lead registrations used alone After control recording, a 3 sec CSP during sinus rhythm was repeatedly applied to the left and right carotid sinus in turn with 1 minute pauses between tests Following a ten minute stabilization period five series of atrial stimulation (AST) with rates ranging 80 to 200 b p m and a 2 msec constant current pulse at approximately two times atrial diastolic threshold were applied for 1 minute each (overdrive) [23] Atrial electrograms and/or His bundle recordings were subsequently registered for at least 1 minute after the interruption of AST (overdrive suppression) [1] The investigation was repeated 2 minutes after the intravenous application of atropine 1 mg Restudy after 16 months in 16 patients who had meanwhile undergone therapeutic pacemaker application, required the temporary suppression of the impulse emission of the implanted unit This was accomplished by electrical chest wall stimulation during testing [4]

Calculations

The control P P interval was averaged from 30 beats P P intervals were measured from the CSP ECGs up to 30 sec following CSP The maximal CSP result was used for evaluation (CSP max) Maximal corrected sinus node recovery time (CSRT max) [7] was calculated as maximal P P interval after AST (= maximal sinus node recovery time) minus mean P P interval at rest Abnormalities of the first post pacing cycle (CSRT max ≧ 560 msec)[27] and secondary pauses [4, 27] were identified and accepted as diagnostic criterion for SSS Cases with atrial premature depolarizations or junctional escape beats with atrial capture were considered, provided they occurred at least 1 4 sec following postdrive

Table II Summary of electrophysiologic findings (mean ± SEM)

Groups	Number of cases	Age (years)	Before atropine HR (bpm)	Before atropine CSP (msec)	Before atropine $CSRT_m$ (msec)	After atropine HR (bpm)	After atropine HR delta (%)	After atropine CSP_m (msec)	After atropine $CSRT_m$ (msec)
HCSR	103	59 9	59 ?	5?96	249 3	79 7	33 8	1328	231
(I)		±1 0	±0 9	±179	±15 5	±1 5	±2 1	±4?	±13
HCSR + SSS	33	60 6	58 4	516?	3488	75 6	27 9	12?0	3015
(II)		±1 8	±2 0	±231	±267	±2 6	±2 6	±184	±553
SSS	30	55 3	58 9	1690	3603	74 7	28 3	1233	3818
(III)		±2.5	±? 5	±1?	±402	±2 8	±? 9	±84	±455
Controls	20	57 3	66 8	1?70	?62 0	8? 4	33 1	1132	234 0
(IV)		±2 4	±1 4	±110	± 9 2	±2 8	±4 1	±49	±8 3

= $p < 0 05$
= $p < 0 01$ P ? es ?s Controls
= $p < 0 001$ n ?l instances.

cardiac standstill Statistical evaluation was carried out using the *t* test for paired and unpaired data

Results

A Clinic Syncope without dizziness was found in 9 to 18 per cent of the patients in the three groups with symptomatic sinus node dysfunction (Table I) The combination of both syncope and dizziness was rather frequent in all three groups (41 to 45 per cent) Dizziness without syncope was present in 25 to 36 per cent of the patients studied Several patients in all groups complained of an inability to concentrate only tiredness or apathy Most patients in group IV suffered either slight dizziness off and on or an inability to concentrate and forgetfulness

As regards additional diseases coronary heart disease (37 to 42 per cent) and hypertension (14 to 36 per cent) were maximally represented in all three groups followed by chronic pulmonary diseases (3 to 9 per cent) and congenital heart disease (2 to 11 per cent)

Routine ECG registrations in all three groups (Table I) revealed a maximal occurrence of S A block and/or S A arrest (15 to 63 per cent) followed by intraventricular conduction disturbances (16 to 36 per cent) and premature atrial contraction (6 to 43 per cent) intermittent atrial fibrillation (21 to 27 per cent) and premature ventricular contractions (18 to 26 per cent) Paroxysmal atrial tachycardias (8 to 21 per cent) intermittent atrial flutter (2 to 19 per cent) and first degree AV block (10 to 14 per cent) were observed less frequently in all three groups There was a prevalent occurrence of S A block and premature atrial contractions in group III intra ventricular conduction disturbances in group I and atrial flutter and paroxysmal atrial tachy cardia in both groups II and III compared to the rest of the groups

B Electrophysiology The results of electro physiologic testing are presented in Table II Groups I to III showed no difference in age compared to controls ($p > 0 05$) Heart rate at rest was slower in group I ($p < 0 001$) group II ($p < 0 01$) and group III ($p < 0 01$) compared to controls CSP was used to separate group I and group II from group III and was 5 3 sec for group I and 5 2 sec for group II Group III had a CSP max value of 1 7 sec which is within the normal range ($p > 0 05$) CSRT which was used to sepa rate group II and III from group I was 0 25 sec in group I considered normal ($p > 0 05$) Group II had an average CSRT of 3 5 sec group III of 3 6 sec

C Atropine study After atropine heart rate at rest was 79 b p m in group I 76 b p m in group II and 75 b p m in group III All values for heart rate were significantly slower than those of controls (see Table II) CSP max after atropine was no longer prolonged in groups I to III compared to controls ($p > 0 05$) CSRT max was 0 23 sec in group I ($p < 0 05$ vs controls) but 3 0 and 3 8 sec in groups II and III ($p < 0 001$) Heart rate increased by 34 per cent in Group I 28 per cent in group II and 28 per cent in group III All these changes were not different from those of controls ($p > 0 05$)

D Clinical correlations (Fig 1) No significant

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(I)		±1 0	±0 9	±1,9	±15 5	±1 5	±2 1	±42	±13
HCSR + SSS	33	60 6	58 4	5162	3488	75 6	27 9	1270	3015
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SSS	30	55 3	58 9	1690	3603	74 7	28 3	1233	3818
(III)		±2 5	±2 5	±17	±40?	±?8	±?9	±84	±455
Controls	20	57 3	66 8	1, 0	26? 0	87 4	33 1	1132	234 0
(IV)		±2 4	±1 4	±110	± 9 2	±2 8	±4 1	±49	±8 3

= p < 0 05
= p < 0 01 P alues vs Controls
= p < 0 001 in all instan es

cardiac standstill Statistical evaluation was carried out using the t test for paired and unpaired data

Results

A Clinic Syncope without dizziness was found in 9 to 18 per cent of the patients in the three groups with symptomatic sinus node dysfunction (Table I) The combination of both syncope and dizziness was rather frequent in all three groups (41 to 45 per cent) Dizziness without syncope was present in 25 to 36 per cent of the patients studied Several patients in all groups complained of an inability to concentrate only tiredness or apathy Most patients in group IV suffered either slight dizziness off and on or an inability to concentrate and forgetfulness

As regards additional diseases coronary heart disease (37 to 42 per cent) and hypertension (14 to 36 per cent) were maximally represented in all three groups followed by chronic pulmonary diseases (3 to 9 per cent) and congenital heart disease (2 to 11 per cent)

Routine ECG registrations in all three groups (Table I) revealed a maximal occurrence of S A block and/or S A arrest (15 to 63 per cent) followed by intraventricular conduction disturbances (16 to 36 per cent) and premature atrial contraction (6 to 43 per cent) intermittent atrial fibrillation (21 to 27 per cent) and premature ventricular contractions (18 to 26 per cent) Paroxysmal atrial tachycardias (8 to 21 per cent) intermittent atrial flutter (2 to 19 per cent) and first degree AV block (10 to 14 per cent) were observed less frequently in all three groups There was a prevalent occurrence of S A block and premature atrial contractions in group III intra ventricular conduction disturbances in group I and atrial flutter and paroxysmal atrial tachy cardia in both groups II and III compared to the rest of the groups

B Electrophysiology The results of electro physiologic testing are presented in Table II Groups I to III showed no difference in age compared to controls ($p > 0 05$) Heart rate at rest was slower in group I ($p < 0 001$) group II ($p < 0 01$) and group III ($p < 0 01$) compared to controls CSP was used to separate group I and group II from group III and was 5 3 sec for group I and 5 2 sec for group II Group III had a CSP max value of 1 7 sec which is within the normal range ($p > 0 05$) CSRT which was used to sepa rate group II and III from group I was 0 25 sec in group I considered normal ($p > 0 05$) Group II had an average CSRT of 3 5 sec group III of 3 6 sec

C Atropine study After atropine heart rate at rest was 79 b p m in group I 76 b p m in group II and 75 b p m in group III All values for heart rate were significantly slower than those of controls (see Table II) CSP max after atropine was no longer prolonged in groups I to III compared to controls ($p > 0 05$) CSRT max was 0 23 sec in group I ($p < 0 05$ vs controls) but 3 0 and 3 8 sec in groups II and III ($p < 0 001$) Heart rate increased by 34 per cent in Group I 28 per cent in group II and 28 per cent in group III All these changes were not different from those of controls ($p > 0 05$)

D Clinical correlations (Fig 1) No significant

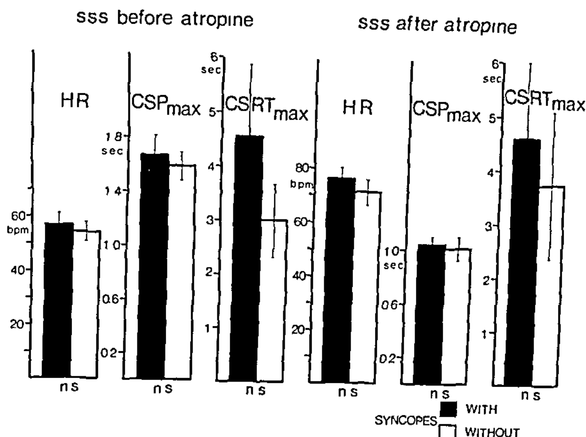


Fig 1 The graph demonstrates no significant differences in SSS patients exemplary for groups I to III between *electrophysiologic* data in patients with syncope *(black columns)* compared to patients without syncope *(light columns)* This indicates that electrophysiologic testing establishes diagnoses but fails to predict severe clinical symptoms in symptomatic sinus node dysfunction Mean ± SEM for all measurements

differences were found for heart rate, CSP max and CSRT max, both before and after atropine ($p > 0.05$) when for each of groups I to III, values of patients with histories of syncope versus those without were separately compared This is graphically exemplified for group III (Fig 1)

E Restudy of SSS A restudy of 16 additional cases of SSS (cases Nos 2 6, 14, and 15 had HCSR as well) was carried out 16 months after the initial study and pacemaker application There were no significant differences in heart rate CSP max and CSRT max, either before or after atropine when the results of the first and the second study were compared No differences could be ascertained for patients with histories of syncope versus those without when heart rate CSP max and CSRT max were compared 16 months after the initial study The values (mean ± SEM) versus those 16 ± 2 6 months later (before atropine) were as follows HR (58 ± 3 b p m vs 54 ± 2 b p m $p > 0.05$) CSP max (2 0 ± 0 4 sec vs 1 9 ± 0 3 sec $p > 0.05$) and CSRT max (4 6 ± 1 2 sec vs 5 8 ± 1 4 sec $p > 0.05$) The values versus those 16 ± 2 6 months later (after atropine) were as follows HR (74 ± 4 b p m vs 70 ± 3 b p m, $p > 0.05$) CSP max (1 1 ± 0 08 sec vs 1 1 ± 0 06 sec, $p > 0.05$) and CSRT max (5 6 ± 1 5 sec vs 6 2 ± 1 4 sec $p > 0.05$)

Discussion

A Methods Some methodological problems need discussion Although many investigative protocols for the study of SSS use the technique of His bundle electrocardiography,[9, 10, 17, 27, 30, 32, 34] diagnostically sound information can be obtained by the use of atrial electrograms and simultaneous multiple surface ECG leads[20, 24, 26, 28] such as were employed in the majority of cases in this study However since a considerable number of patients with the Sick Sinus Syndrome have disease of the distal conduction system the use of a His bundle electrocardiogram is useful in detecting such patients

The CSRT values appear long in this study Since methods of calculating CSRT vary the average lengths of prolonged CSRT in the literature vary as well at about 2 8 to 5 cm CSRT is long when spontaneous postpacing atrial depolarization of sinus origin and/or late retrograde

junctional activity are accepted as sinus node recovery [8, 25, 29] and CSRT is shorter (< 3 sec) when any ectopic postpacing atrial deflection is also taken as sinus recovery [7, 8, 9, 1, 2] Since direct measurement of sinus node activity is not available the actual sinus recovery might of course have occurred any time between a late postdrive junctional escape beat and an even later occurring P of ectopic origin and have just been suppressed by retrograde activity

It should be considered that only a limited number of patients with SSS have an abnormal CSRT borne out by previous studies [1, 2, 27, 32] in which prolonged CSRT in 56 per cent (35 to 93 per cent) of the patients with symptomatic sinus node disease was found Such false negative responses of atrial tachy pacing have been attributed to the failure of consistent depolariza tion of the sinus node by the paced atrial beats due to entrance block [16, 7, 3] To minimize such errors we followed recommended techniques that included assessing prior to diagnostic AST sequences the reset of S A node by an initial run of atrial pacing at rates lower than the intrinsic sinus rate at rest using six sequences of different AST rates in overdrive testing to increase the chance of stimuli penetrating the atrium and the S A node [3, 27] should an optimal rate for pene tration of temporary entrance block exist [6, 3] repeating all AST runs after the application of atropine (thought to abolish entrance block) [17] However our group II and III patients who were selected on grounds of pathologic CSRT alone might still not be representative for all patients with symptomatic sinus node disease

B Electrophysiological data In contrast to group II (HCSR + SSS) isolated SSS patients (group III) did not show positive CSP reaction Some authors found positive CSP response the major manifestation of sinus node dysfunction in 13 per cent of their cases with sinus node disease and a poor atropine response independent of the carotid sinus reflex was suggested as evidence of sinus node dysfunction This view is not supported by our findings Heart rate was found to be identical in all three groups but signifi cantly slower compared to controls (Table II) After atropine the relative increase of heart rate for all groups was about 31 per cent and was identical to that of controls ($p > 0\,05$) However evaluated absolutely heart rate of all groups was again significantly lower compared to controls ($p < 0\,05$) Atropine normalized all CSP induced asystoles ($p > 0\,05$) but left unchanged patho logically increased CSRT max values In our opinion vagal activity alone cannot adequately explain such findings We conclude that an increased vagal tone is primarily responsible for the CSP induced bradycardias and asystoles While an organic S A node destruction and/or disturbance of sinoatrial conduction should be postulated for group II (HCSR + SSS) and group III (isolated SSS) a decreased catecholamine response might be discussed for the group with isolated HCSR With appropriate testing HCSR and SSS are apparently separable entities and the combination of both syndromes occurs rather frequently All three groups in our study present slower resting heart rates which could be but one hallmark for symptomatic sinus node disease To what degree the increased vagal tone is respon sible for this bradycardia remains open to further investigation

C Correlation of symptoms and electrophysi ology In our population of symptomatic patients with sinus node dysfunction about 50 per cent complained of syncopal attacks This rather high percentage is similar to that (50 per cent ± 14 per cent) found by previous investiga tors [6, 2, 3, 3, 39, 45] When patients in this study with syncope were compared to patients without syncope no differences within the three groups between heart rate duration of CSP max and CSRT max results before and after atropine were found We consider this to be a most important result since we found that patients with severe symptoms cannot be separated from patients with mild symptoms using electrophysiologic testing This implies that spontaneous arrhyth mic disturbances causing severe symptoms can not be predicted from careful electrophysiologic studies The clinical dilemma of indication of pacer application cannot be solved by comparison of electrophysiologic data

Attempts to classify SSS according to degrees of severity take different approaches in different investigations and they are far from being system atic Apparently pacemaker treated series are composed of patients with severe symptoms and may not be representative All attempts thus far to identify subgroups of SSS have proven statisti cally unreliable [3, 6, 1, 1, 0, 2, 32, 3, 3, 35] as did ours in the present study This implies that in each case questionable symptoms need to be

meticulously tested and pacer therapy applied liberally, since, although death is more likely due to secondary events rather than the syncopal attack, virtually even asymptomatic patients with pathologic test results can become the victim of their first syncope[43]

The time interval between the occurrence of apparently minor symptoms and syncope in patients with sinus node dysfunction may extend beyond 5 years This observation agrees with other investigations[6 15 8 31 33] However, reports regarding the natural history, prognosis and follow up in SSS are rare in the literature and usually consist of mere prognostic observations without actual electrophysiologic restudies in sinus node dysfunction In this study, which is we believe the first of its kind there was no significant change in CSRT max, CSP max and heart rate before and after atropine application within a period of 16 months between the initial study and the restudy of 16 cases with SSS This implies poor prognosis in SSS and confirms the results of Gupta and associates[17] and Narula and colleagues[7] who reported CSRT was reproducible after 7 5 months (6 months respectively) in one of their patients

Summary

The relation of hypersensitive carotid sinus syndrome (HCSR) to sick sinus syndrome (SSS) is not clear vagal role relevance of electrophysiological testing and the natural course of both syndromes are ill defined In 186 symptomatic patients resting heart rate (HR) carotid sinus pressure results (CSP) and corrected sinus node recovery time (CSRT) were determined before and after atropine (A) According to test results 102 patients had HCSR (group I) 33 had HCSR + SSS (group II) 30 patients had isolated SSS (group III) and 20 served as control (group IV) HR below 60 b p m in groups I to III and lower than controls ($p < 0\ 01$) rose after A by approximately 31 per cent in groups I to IV This indicates predominant vagal tone and establishes that rate response to A is unreliable as a diagnostic test for groups I to III CSP normalized after A but CSRT remained unchanged ($p > 0\ 05$) which implies increased vagal tone in HCSR but destructive affection of the SA node in SSS Bradycardia, S A block supraventricular tachyarrhythmias and the combination of dizziness and syncope served as diagnostic clues for HCSR or SSS in a limited number of patients CSP and CSRT separated HCSR from SSS but failed to predict syncope in groups I to III ($p > 0\ 05$) and thereby cannot aid the indication for pacer application SSS test results remained unchanged over 16 months showing an unfavorable prognosis We conclude that HCSR and SSS although frequently occurring together are entities made separate by specific testing which however, fails to aid in therapeutic decision making Vagal tone plays but one role in HCSR and SSS and electrophysiologic pathology of SSS does not improve in its course

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Differences in metal content of the heart muscle in death from ischemic heart disease

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The increased death rate from ischemic heart disease in soft water areas suggested that the mineral salt concentration in the drinking water affected the death rate from ischemic heart disease, and that there was a specific effect on the heart muscle [1] Since the increased death rate in soft water areas seems to be due to an increase in sudden deaths, the metal content of the heart muscle in those dying suddenly from ischemic heart disease is of particular interest

We have shown that there is a significant decrease in magnesium concentration in the heart muscle of those dying suddenly from ischemic heart disease [3] This was confirmed by Behr and Burton [4] who found that although there was a decrease in magnesium in the heart muscle in those dying suddenly from heart disease there was no decrease in chronic heart disease or in the skeletal muscle of those dying suddenly Anderson and co workers[5] have confirmed the decrease in magnesium in death from heart disease They also found a significant increase in the calcium concentration and a decrease in the copper concentration in the heart muscle of those dying from ischemic heart disease but no significant differences in the concentrations of zinc chromium cadmium and lead

We have reported separately some work on the concentrations of silicon and aluminum in the heart muscle of those dying suddenly from ischemic heart disease [6] This report compares the concentrations of several metals of interest in the heart muscle from three different groups one control group of patients with apparently normal heart muscle, a group of late heart deaths, and a sudden' heart death group The causes of death in the normal control group included accidental and suicide deaths, pneumonia and some deaths from cancer We have shown that there was no significant difference in magnesium concentration of accident and suicide deaths as compared to those from sudden and chronic illness unrelated to heart disease [7] The late death group represented chronic heart disease and these were defined as patients who had suffered a coronary thrombosis and died more than three months later The sudden death group were defined as in our previous report [3]

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Materials and methods

Samples of left ventricle were taken at necropsy and in the deaths from ischemic heart disease were from uninfarcted areas of the ventricle All the sudden death samples and some of the normal control group came from the Hull City Mortuary they were stored at 4° C for 1 to 3 days then stored at −20° C until they were prepared for analysis All the late death samples and the other normal control samples came from the Hull Royal Infirmary and were stored at −20° C immediately after necropsy There was no significant difference between the normal samples from these two different sources

Samples of heart muscle were wet ashed as described previously [3] The sulphuric acid which was present in solutions prepared by the wet ash method interfered in analyses for calcium For calcium analyses samples of ventricular muscle (*ca* 5 Gm) in platinum crucibles were dried to constant weight at 100° C and were then ashed in a muffle furnace at 450° C The ash was dissolved

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Table I Metal concentrations in heart muscle

		Sudden heart death			*Late heart death*			*Normal controls*		
		All	*Male*	*Female*	*All*	*Male*	*Female*	*All*	*Male*	*Female*
Magnesium	Conc (µg/Gm wet weight)	154	[illegible]	[illegible]	173	170	175	186	181	190
	S D	27	29	22	17	20	[illegible]	[illegible]	28	22
	Number	59	43	16	22	9	13	158	72	86
Calcium	Conc (µg/Gm wet weight)	57.0	56.9	57.4	43.1	39.8	45.3	39.0	42.6	36.1
	S D	26.0	26.2	26.2	15.8	6.5	19.9	22.9	25.2	20.7
	Number	59	43	16	22	9	13	129	57	72
Sodium	Conc (µg/Gm wet weight)	906	[illegible]	937	947	[illegible]	942	929	903	[illegible]
	S D	326	346	[illegible]	223	227	229	222	255	190
	Number	59	43	16	22	9	13	158	72	86
Potassium	Conc (µg/Gm wet weight)	[illegible]	1490	1830	2130	2160	2110	2080	1870	[illegible]
	S D	[illegible]	690	530	370	[illegible]	300	[illegible]	680	680
	Number	36	27	9	22	9	13	158	72	86
Iron	Conc (µg/Gm wet weight)	38.5	37.6	41.6	48.6	51.4	46.6	46.8	[illegible]	47.8
	S D	11.0	10.9	10.8	8.1	9.3	6.8	9.6	11.0	8.1
	Number	36	28	[illegible]	22	9	13	158	72	86
Copper	Conc (µg/Gm wet weight)	3.11	3.08	3.19	2.84	2.77	2.88	3.32	3.30	[illegible]
	S D	0.44	0.48	[illegible]	0.36	[illegible]	0.38	0.66	[illegible]	0.63
	Number	31	23	8	22	9	13	[illegible]	31	25
Manganese	Conc (µg/Gm wet weight)	0.96	0.97	0.91	[illegible]	0.72	0.60	1.07	1.15	0.96
	S D	0.18	0.19	0.15	0.23	0.21	0.25	0.31	0.36	0.20
	Number	31	23	8	22	9	13	56	31	[illegible]
Magnesium/ calcium	Ratio	3.60	3.60	3.58	4.40	4.42	4.37	6.13	5.72	6.46
	S D	2.35	[illegible]	2.11	1.32	1.12	1.49	2.64	2.71	[illegible]
	Number	59	43	16	22	9	13	129	57	72
Age	Mean	66.5	64.3	[illegible]	[illegible]	64.3	[illegible]	[illegible]	55.4	60.4
	S D	9.9	9.6	8.1	11.8	[illegible]	9.5	20.7	20.5	[illegible]
	Number	59	43	16	22	9	13	158	72	86

in the minimum quantity of hydrochloric acid Appropriate quantities of the wet ash (Mg Na K Fe Cu^{2+} Mn^{2+}) or dry ash (Mg Ca^{2+} Na K Fe Cu^{2+} Mn) solutions were analyzed by atomic absorption spectrophotometry using a Perkin Elmer Model 305B spectrophotometer with an air/acetylene flame Analyses for magnesium sodium potassium manganese and copper of solutions prepared by wet ashing and dry ashing the same sample gave excellent agreement Analyses for iron on wet ashed samples were corrected for the blank reading found for this element

Results

The concentrations of lithium lead chromium cobalt strontium cadmium and mercury in our solutions were so low that they were not measurable by flame atomic absorption techniques Table I gives the concentrations (in µg/Gm wet weight) of magnesium calcium sodium potassium iron manganese and copper in our three groups and Fig 1 indicates the percentage difference from the normal control group in the two heart death groups for all these elements and for the magnesium/calcium ratio

There was a highly significant ($t = 8.14$)

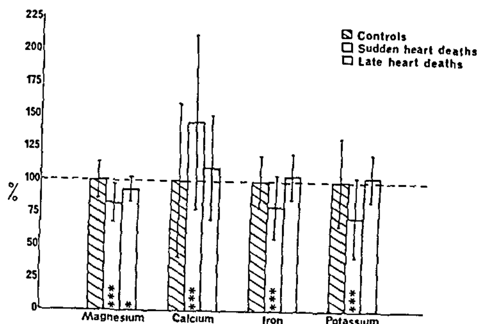


Fig 1 Comparative metal concentrations of heart muscle (controls = 100 per cent) *Bar lines* show standard deviations probably significant 0 05 > P > 0 01 significant 0 01 > P > 0 001 highly significant 0 001 > P

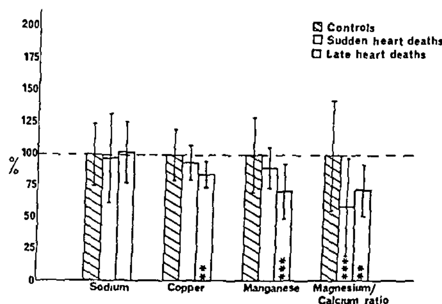


Fig 1 B For legend see above

decrease in the magnesium concentration in the sudden death group as expected from earlier work This difference was still highly significant (t = 5 33) when normal males were compared with males from the sudden heart death group and when normal females were compared with females of the sudden heart death group (t = 5 14) There was a much smaller decrease in magnesium in the late death group which was only significant at the 5 per cent level (t = 2 30) and was only probably significant in females (t = 2 34) when the sexes were considered separately

There was no significant difference between the calcium concentrations of the normal and late death groups but the sudden death group showed a highly significant (t = 4 81) increase in calcium The difference in females was also highly significant (t = 3 55) but in males the difference was only significant at the 1 per cent level (t = 2 77)

For both potassium and iron concentrations there was no significant difference between the normal and late death groups but a highly significant decrease in the sudden death group (t = 4 10 for potassium 4 58 for iron) The potas

sium in normal males was significantly ($t = 3.55$) lower than in normal females. When males and females were considered separately, the decrease in potassium in the sudden death group was only probably significant for the males ($t = 2.42$) and not significant for the females ($t = 1.81$). The decrease in iron concentration was still significant when males and females were considered separately, though t was higher for the males (3.32) than for the females (2.10).

The results for copper and manganese concentrations were very different from those for the other elements. The slight decrease in both elements in the sudden death group was not statistically significant, but the late death group showed a highly significant decrease in manganese ($t = 4.24$) and a significant difference in the copper concentration ($t = 3.21$). When males and females were considered separately, the decreased manganese in the males was significant at the 1 per cent level ($t = 3.39$) and the other comparisons were all probably significant.

There was no significant difference in the magnesium/potassium ratio between the groups, but a highly significant decrease in the magnesium/calcium ratio of the sudden death group compared with the normals ($t = 6.30$). The decreased magnesium/calcium ratio in the sudden death group was highly significant for both males ($t = 4.02$) and females ($t = 4.18$) compared separately. This ratio was also significantly decreased in the late death group compared with the normal group ($t = 3.00$), but was only significant in females ($t = 2.84$) when the sexes were compared separately.

The differences between the sudden death and late death groups were highly significant for the potassium concentration, significant for the magnesium, iron, manganese, and copper concentrations, and probably significant for the calcium concentration.

Measurements of the water content of some of the heart muscle samples indicated that there was no significant difference in the water content of the heart muscle from the three groups, so that these wet weight comparisons are also valid as indications of the relative concentrations per gram dry weight.

Statistical analysis indicated that there was no significant variation with age for the concentrations of any of the elements. Histograms of the results indicated that the distributions were reasonably normal, and Wilcoxon Mann Whitney significance tests gave similar results to the t tests.

Discussion

A general feature of our results is the similarity of the late heart death group to the normal control group, apart from the significant decreases in manganese and copper concentrations and the magnesium/calcium ratio in the late heart death group. This suggests that, other factors being equal, the concentrations of some metals in the heart muscle may be important in deciding whether a patient survives a coronary thrombosis.

In the sudden heart death group there were significant decreases in the concentration of magnesium, potassium, and iron and a significant increase in the concentration of calcium. The decrease in magnesium confirms the results from earlier studies.[3,5] Seelig has suggested that the Western diet is deficient in magnesium and that lack of magnesium may be a cause of the increased death rate from ischemic heart disease in soft water areas,[9,10] and Bradshaw and Dean[11] have suggested that a prospective study of those regularly taking magnesium salts should be carried out to show whether magnesium has a specific protective effect in ischemic heart disease. Anderson and colleagues[5] found that the magnesium concentration of normal heart muscle was slightly lower in soft water areas of Canada compared with hard water areas, whereas our comparison of English hard and soft water areas showed the reverse.[12] We suggested that possibly the magnesium/potassium ratio, which was lower in the soft water area, might be important in susceptibility to death from ischemic heart disease. In the present survey, however, there is no significant difference in magnesium/potassium ratio between the sudden death group and the normal group.

Previous studies of both animals and men have usually found a decrease in potassium accompanying the decreased magnesium in hearts affected by ischemic heart disease and related conditions. Our earlier investigation[3] showed a slight but not statistically significant decrease in potassium concentration in the hearts of those dying suddenly from ischemic heart disease and

in this larger study the potassium concentration in the sudden heart deaths was significantly reduced There was a negative correlation between the cardiovascular mortality rate in South Wales and the potassium content of the drinking water, but Elwood, Abernethy, and Morton[13] considered that this was negligible as compared with the correlation with the calcium content of the drinking water In comparing normal hearts from Hull and Burnley, we found that there was a significant increase in the potassium concentration in the heart muscle samples from the soft water area (Burnley),[12] which makes it unlikely that any increased death rate in soft water areas is directly related to potassium metabolism

Calcium also seems to be ruled out as the 'water factor" by these results Our sudden death group, like the Canadian heart deaths, had a significantly increased calcium concentration, which makes it unlikely that the decreased calcium content of soft water is the factor increasing heart deaths It is not likely that this higher calcium is due to deposition of calcium salts in atheromatous plaques, since there was no significant increase in the calcium in our late death group where such deposits might also be expected Since there are established interrelations between calcium and magnesium,[14] it is possible that, as suggested by Anderson and associates[5] the increased calcium in the sudden heart deaths may be secondary to the decrease in magnesium concentration Calculations on Anderson and colleagues data[5] show that there is a highly significant decrease in the magnesium/calcium ratio in the heart deaths in the Canadian survey, like the decrease in this ratio we report here In the soft water areas the magnesium/calcium ratio in the heart deaths was 2 47 while in the accident cases it was 4 10 ($t = 7\ 45$), in the hard water areas the ratio in heart deaths was 2 47 and the accident death ratio was 4 23 ($t = 5\ 04$) The slight decrease in the accident deaths in the soft water area was not statistically significant, but it is in the direction one would expect if this ratio change contributed to the increased death rate in soft water areas This ratio may vary in different populations as the means in our investigation are nearly 50 per cent greater than the values for the corresponding Canadian groups

The decreased iron concentration in the sudden heart death group is unexpected The iron will be almost entirely bound in the heme groups of myoglobin and the cytochromes[15] These proteins are most unlikely to leak out of cells after death as might occur with the small cations, so the iron decreases must have occurred before death Decreases in the concentration of these heme proteins will decrease the cell s capacity to react with oxygen and thus the rate of production of adenosine triphosphate will be lower A lower capacity to produce adenosine triphosphate may be a great disadvantage in conditions of oxygen shortage after a myocardial infarction

We found a decrease in copper concentration for the late heart death group but not for the sudden heart death group Anderson and coworkers[5] found a decrease in copper concentration in the heart muscle of those dying from ischemic heart disease About 85 per cent of their heart deaths occurred less than 24 hours after the first symptoms so their patients could be considered as intermediate between our sudden and late death groups Severe copper deficiency has been associated with effects on the heart in cows and pigs[16] Our results suggest that copper deficiency is not important in those dying suddenly from ischemic heart disease, but may be important to those who survive the initial myocardial infarction

Although we found a decrease in manganese in the late deaths the total concentration of this element is very small Manganese can normally replace magnesium *in vitro* as an activator of enzymes acting on adenosine triphosphate so the decrease in manganese may add to the harmful effects of the slight decrease in magnesium in the late deaths Cardiovascular mortality has been shown to have a positive association with manganese in water,[13] however, which suggests that manganese may have a harmful effect on the heart

These results suggest that the factor most likely to increase the death rate in soft water areas may be a decrease in the magnesium/calcium ratio as these two cations are vitally important in the control of muscular contraction[17] The iron concentration in the heart was not measured in the Canadian study and Elwood Abernethy and Morton[13] did not report on the iron concentrations in their water samples It is possible that a decrease in the iron in the heart muscle in soft water areas might also

contribute to the increased death rate Preliminary results[6] suggest that possible toxic effects from aluminum are also worth investigation

The sudden heart death group showed significant decreases in the concentration of magnesium iron and potassium Decreases in magnesium iron and potassium have recently been established in Kwashiorkor[18] Magnesium deficiency has been particularly associated with the electrocardiographic changes in Kwashiorkor[9] and in alcoholic heart disease[20] Sudden death from ischemic heart disease may be another result of empty calorie malnutrition Diets which are high in fats and refined carbohydrates will probably be low in mineral salts[21] It is therefore possible that the harmful effect of Western diets on ischemic heart disease rates is not due to the increase in saturated fats cholesterol or sucrose but to a deficiency of mineral salts This deficiency could lead to the decreased concentration of several vital metals we have observed in those dying suddenly from ischemic heart disease

Summary

In a group of patients dying suddenly from ischemic heart disease the uninfarcted heart muscle contained significantly lower concentrations of magnesium iron and potassium and a significantly higher concentration of calcium than the heart muscle from a group of normal controls and a group of patients dying more than three months after a coronary thrombosis The late death group had significantly lower concentrations of manganese and copper than the normal group and a slight decrease in magnesium concentration which was probably significant There was no significant difference in the sodium concentration between the three groups

The results are discussed in relation to the increased death rate from ischemic heart disease in areas with soft drinking water and possible dietary deficiencies in mineral salts

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The effect of chronic cardiac denervation on infarct size following acute coronary occlusion

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The autonomic nervous system exerts considerable influence on the heart and coronary circulation While this influence is beneficial to the function of the normal heart during coronary insufficiency autonomic stimulation may be detrimental to the viability of ischemic myocardium Thus following acute coronary occlusion, infarct size is reduced by beta adrenergic blockade[1-4] and increased by beta adrenergic stimulation[4-6] The deleterious effect of beta adrenergic stimulation on ischemic myocardium is generally attributed to the actions on contractile force heart rate, and secondarily on oxygen demand However a full understanding of the mechanisms involved is obscure[7,8] Alpha adrenergic mechanisms may also be involved in a detrimental effect of autonomic stimulation on the myocardium during coronary insufficiency The coronary vasculature is under the influence of both an alpha adrenergic constrictor tone and an opposing beta adrenergic dilator tone[1] Although under normal conditions the beta adrenergic effect on the coronary vasculature predominates alpha adrenergic activity may increase under certain conditions For example, alpha adrenergic activity is increased during some forms of coronary insufficiency in humans[1] and there is evidence that during experimental coronary occlusion alpha adrenergic activity limits collateral flow to ischemic myocardium[11] The coronary vasculature is also innervated by vagal cholinergic fibers which produce vasodilatation,[1] but little is known about the importance of cholinergic influences during coronary insufficiency

In earlier studies various forms of cardiac denervation have been used to examine the effects of neural influences on the viability of the myocardium following coronary occlusion and the results are contradictory[13-18] In recent studies using a complete cardiac denervation model we observed dramatic differences between the myocardial response to coronary occlusion in dogs which had undergone denervation 2 weeks prior to the experiment and that in control non denervated dogs[1] In non denervated hearts occlusion of a coronary artery caused contractile force in the muscle supplied by that artery to be reduced by approximately 65 per cent In denervated hearts contractile force was reduced by only 13 per cent Furthermore, in non denervated hearts an intense cyanosis always developed rapidly in the involved muscle On the contrary in denervated hearts cyanosis was never observed indicating a substantial collateral flow to the myocardium normally supplied by the occluded vessel On the basis of these results the present studies were undertaken to examine more closely the effects of chronic cardiac denervation on the myocardial response to acute coronary occlusion

Methods

Mongrel dogs of either sex, weighing 14 to 30 kilograms and anesthetized with intravenously administered sodium pentobarbital (30 mg/kg

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body weight) were used Two studies were performed as follows

Infarct size study In these experiments four groups of dogs were used These consisted of (1) 10 acute controls which were non denervated (2) six acutely denervated dogs in which the heart was denervated immediately prior to coronary occlusion and in which adrenergic blockade was maintained pharmacologically (3) seven chronically denervated dogs in which the heart had been denervated 2 weeks prior to the experiment and (4) four sham operated dogs which 2 weeks prior to the experiment had been subjected to a surgical procedure similar to that involved in chronic cardiac denervation but in which the cardiac nerves had not been cut

For acute cardiac denervation experiments a femoral artery in each animal was catheterized with a fluid filled Tygon catheter and the catheter tip was positioned in the thoracic aorta This catheter was connected to a Statham P23AC pressure transducer and the transducer was connected to a Grass model 7D Polygraph for continuous display of arterial pressure (AP) The AP signal was used as the input to a Grass model 7P1F tachograph for display of heart rate (HR) A second Tygon catheter was inserted into a femoral vein for administration of drugs Each dog was artificially respired with a Harvard model 615 respirator and the chest was entered through the fourth intercostal space on the left side using an electrosurgical unit The caudal cervical ganglia on each side were stripped and the thoracic vagi as well as the dorsal and ventral ansae were sectioned Since the myocardial catecholamine level is still high following acute denervation and since there may be intramyocardial adrenergic reflexes not involving extrinsic nerves[20] both an alpha and a beta adrenergic antagonist were administered To do this a test dose of 0 4 µg/Kg body weight norepinephrine was injected and the HR and AP responses were noted The beta adrenergic antagonist propranolol (1 mg /Kg body weight) and the alpha adrenergic antagonist phentolamine (1mg /kg body weight) were then administered and the responses to a second dose of norepinephrine were obtained These responses were always abolished immediately after propranolol and phentolomine administration Coronary occlusion was then performed for the infarct size experiment as described below and at 30 minute intervals test doses of norepinephrine were repeated An increase in AP was regarded as evidence of alpha adrenergic stimulation and if this response was seen additional phentolamine (0 3 to 0 5 mg /Kg body weight) was administered An increase in HR indicated beta adrenergic stimulation and when this was seen additional propranolol (0 3 to 0 5 mg /Kg body weight) was injected

In each acute control dog a femoral artery was catheterized and HR and AP were monitored as described above Each animal was artificially respired and the chest was entered through the fourth intercostal space on the left side After AP and HR stablized coronary occlusion was performed for the infarct size experiment

The method used for chronic cardiac denervation has been described previously[21,22] Each dog was artificially respired and using sterile techniques the chest was entered through the fourth intercostal space on the left side The left thoracic vagus nerve (LTV) right thoracic vagus nerve (RTV) left stellate ganglion (LS) and right stellate ganglion (RS) were isolated The pericardium was opened a pericardial cradle formed and Walton Brodie strain gauge arches were sutured to the left atrial appendage and to the base of the left ventricle Recordings of left atrial contractile force (LACF) and left ventricular contractile force (LVCF) were displayed on a Grass polygraph recorder and the output of the LVCF driver amplifier was used as the input to the tachograph for continuous recordings of HR Following stabilization of all recordings the LTV RTV LS and RS were stimulated with a Grass S9 stimulator which delivered square wave pulses of 5 msec duration at a rate of 10/sec and voltages of 4 to 6 v for the vagus nerves and 8 to 10 v for the stellate ganglia Typical control predenervation inotropic and chronotropic responses are illustrated in the top tracings of Fig 1 After obtaining these responses all cardiac nerves were surgically ablated within the pericardium The procedure included a careful transection around the complete circumference of the superior vena cava with ligation and division of the azygous vein The dissection was continued medially from the superior vena cava across the superior surfaces of the right and left atria and pulmonary veins and included section of the ventrolateral cardiac nerve The adventitia was removed from the complete circumference of the pulmonary artery All nervous tissue was also removed from

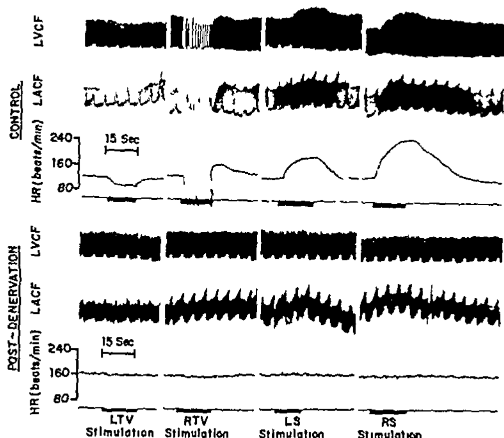


Fig 1 Typical cardiac responses to stimulation of the thoracic vagus nerves and stellate ganglia before *(upper tracings)* and after *(lower tracings)* cardiac denervation by the method used in the chronic denervation experiments *HR* = heart rate *LACF* = left atrial contractile force *LS* = left stellate ganglion *LTV* = left thoracic vagus nerve *LVCF* = left ventricular contractile force *RS* = right stellate ganglion *RTV* = right thoracic vagus nerve

between the roots of the pulmonary artery and the ascending aorta After performing these procedures responses to LTV RTS, LS and RS stimulation were again obtained in order to ascertain that cardiac denervation was complete The lower tracings of Fig 1 show the absence of any inotropic or chronotropic response after a complete denervation When total denervation was assured the strain gauge arches were removed The pericardium was closed and the chest was closed in layers Each animal was allowed to recover and was treated with antibiotic (Longicil 1 ml /10 Kg body weight/day) for 4 days A period of 2 weeks was allowed before experimentation During this time the myocardial catecholamine level presumably was depleted [3,4] Also our previous studies have suggested a substantial protection against infarction after this time [1] After 2 weeks each animal was re anesthetized AP and HR were monitored as described above and the chest was re entered through the fourth intercostal space on the left side Responses to LTV, RTV LS and RS stimulation were again obtained in order to re check the completeness of cardiac denervation Coronary occlusion was then performed for the infarct size experiments as described below

In the sham operated dogs the chest was opened through the fourth intercostal space using sterile techniques A pericardial cradle was formed and strain gauge arches were sutured to the left atrial appendage and to the base of the left ventricle The chest remained open for 3 to 4 hours, at which time the strain gauges were removed and the pericardium and chest were closed These animals were treated with antibiotic and carefully observed for 2 weeks until the day of the experiment

The method used to produce a standardized coronary occlusion and to estimate the resulting infarct size was identical in all groups and has been reported previously [1,23,24] In each animal a pericardial cradle was formed Only animals having a normal left anterior descending artery (LAD) distribution were used in the study Normal LAD distribution was considered to be

present when there were one or more branches of the LAD above the apical branch and when the apical branch originated at approximately the distal end of the middle third of the LAD If these criteria were satisfied two silk ligatures were placed around the LAD immediately above the apical branch When AP and HR had stabilized these ligatures were tied It has been shown that a uniform infarct size can be produced in dogs by occlusion of the LAD in this manner The LAD occlusion was maintained for a period of 6 hours at which time the animal was killed and the heart was immediately excised The atrium the free wall of the right ventricle and all fat were removed from the left ventricle (LV) The LV was then carefully sliced cross sectionally into seven to nine sections approximately 0 7 to 1 0 cm in thickness The sections were incubated at 37 ° C in nitro blue tetrazolium (NBT) solution prepared by mixing 250 mg NBT 80 ml 1M phosphate buffer and 720 ml distilled water After an incubation period of 10 minutes a clear distinction between infarcted muscle and non infarcted muscle was apparent The formazan formed by dehydrogenase activity in the undamaged muscle produced a rich blue color while the infarcted muscle remained unstained The unstained portion of the LV was carefully cut away from the stained portion and weighed The weight of the infarct was compared to total LV weight and expressed as a percentage of total LV weight

Demonstration of non perfused myocardium

In this study two groups of animals were used These consisted of four dogs in which the heart was chronically denervated as described above and four non-denervated controls which had not been subjected to any prior surgery In the denervated dogs the stellate ganglia and vagus nerves were re-stimulated on the day of the experiment to re-check the completeness of denervation Only chronically denervated animals were used since the infarct size studies had already shown that by far the largest effect on infarct size was seen in these animals Also acute controls rather than sham-operated dogs were used since the previous studies had demonstrated no significant difference between infarct size in acute controls and sham operated animals

To demonstrate areas of non perfusion within the myocardium following coronary occlusion

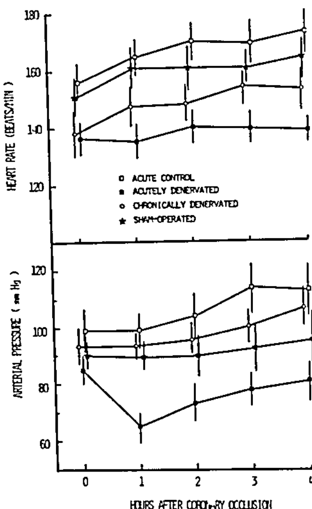


Fig 2 Heart rates and arterial pressures before and following coronary occlusion in the four groups of dogs used in the infarct size study *Vertical bars* are standard errors of the mean.

the vital stain thioflavin S was used[2] This stain binds to endothelium and fluoresces intensely when exposed to ultraviolet light Thus if a tissue is perfused with thioflavin S is sectioned and exposed to ultraviolet light all areas of tissue which received flow will fluoresce while areas which did not receive flow will appear dark. In these experiments the LAD was ligated above the apical branch as described above Five minutes after LAD occlusion 1 ml/Kg body weight of a 4 per cent solution of thioflavin S was injected through a Tygon catheter inserted into the right atrium via a jugular vein After a period of 15 seconds the heart was quickly arrested by injection of concentrated KCl and immediately excised The atria the free wall of the right

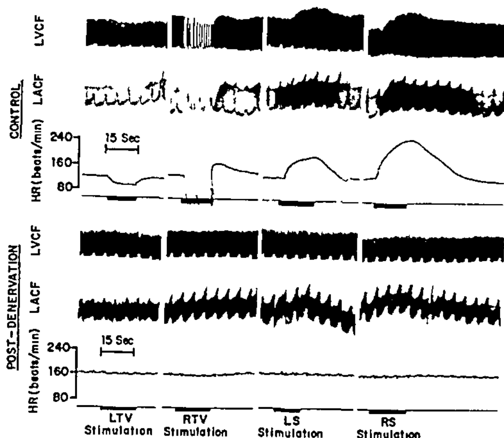


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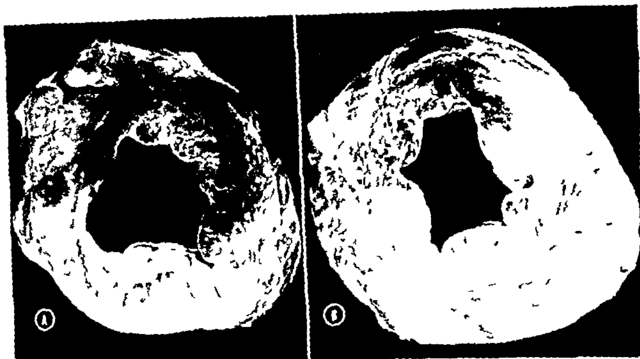


Fig 3 A and B A section of left ventricle obtained from an acute control (A) and a chronically denervated (B) heart comparing the quantity of non perfused myocardium produced by acute coronary occlusion The dark areas are the regions of muscle which were non perfused

the chronically denervated animals mean infarct size in this group was only 3 8 per cent of LV weight It is remarkable that two of the hearts in the chronically denervated group had infarct sizes of less than 1 per cent and five hearts had infarct sizes of less than 4 per cent This large reduction in infarct size following chronic denervation was apparently not due to a promotion of coronary collateral growth caused by the opening of the pericardium and the ensuing irritation of the epicardial surface since the mean infarct size in the sham operated group was not statistically different from that seen in the acute controls

Determination of non perfused myocardium Figs 3A and 3B show typical results obtained from an acute control heart (A) and from a chronically denervated heart (B) The light areas in the heart sections are those areas of the myocardium which were perfused prior to arrest and excision of the heart The dark areas are those portions of myocardium which were not perfused From these photographs it is evident that the quantity of muscle which was non perfused is much smaller in the chronically denervated heart than in the acute control heart The results shown in Fig 3 are exemplary of all animals used in this study with the exception of one dog in the chronically denervated group which showed a slight inotropic response to RS stimulation when the completeness of cardiac denervation was checked on the day of the experiment In this case I VCF was increased 110 per cent when the RS was stimulated prior to the denervation procedure and 20 per cent when the RS was stimulated 2 weeks after the procedure This animal was the only one of the chronically denervated group which showed a residual response to either vagal or stellate stimulation and it is interesting that the size of the non perfused myocardium in this heart was similar to that commonly observed in acute control hearts

Discussion

The results presented in this paper clearly demonstrate that both chronic cardiac denervation and acute denervation with adrenergic blockade result in a substantially reduced infarct size following acute coronary occlusion These results also demonstrate that the protective effect of cardiac denervation is enhanced with time such that the infarct produced by coronary occlusion

Table I Analysis of infarct sizes in acute control acutely denervated, chronically denervated, and sham operated hearts

Dog no	Infarct weight (Gm)	Left ventricular weight (Gm)	% infarct
Acute controls			
10	10 7	53 6	20 0
11	17 3	97 6	17 7
12	18 1	87 8	20 6
13	10 0	46 5	21 5
15	17 0	98 0	17 3
16	14 2	71 6	19 8
20	12 9	75 8	17 0
24	20 0	80 7	24 8
29	13 1	66 3	19 8
40	27 9	126 7	22 0
MEAN	16 1	80 5	20 1
SE	1 7	7 4	0 80
Acutely denervated hearts			
36	18 1	101 1	17 9
37	18 1	103 0	17 6
38	11 7	93 7	12 5
42	9 2	81 2	11 4
43	12 5	67 2	18 6
45	12 2	100 4	12 1
MEAN	13 7	91 1	15 0
SE	1 5	5 8	1 4
P	–	–	0 004
Chronically denervated hearts			
14	5 5	72 4	7 7
17	3 0	97 0	3 1
19	0 5	82 7	0 6
22	8 9	92 4	9 7
25	0 7	87 0	0 8
28	1 1	91 7	1 2
33	1 7	50 8	3 9
MEAN	3 1	82 0	3 8
SE	1 2	6 0	1 4
P	–	–	<0 001
Sham Operated hearts			
26	19 9	97 4	20 5
30	24 9	93 6	26 6
32	19 5	87 4	22 3
35	18 0	123 0	14 7
MEAN	20 6	100 4	21 0
SE	1 5	7 8	2 5
P	–	–	0 633

ventricle and all fat were trimmed from the LV and the LV was sectioned as in the infarct size experiments The LV sections were then photographed under ultraviolet light (360 mμ) using a Tiffen No 12 barrier filter Kloner and co workers[3 11] used thioflavin S to delineate non perfused myocardium after coronary occlusion and quantitated the area of non perfusion by planimetry of the photographic image However we observed that the non perfused muscle was often very nonuniform in distribution such that planimetry was difficult and imprecise Nevertheless large differences in the quantity of non perfused muscle between the non denervated and denervated hearts could be qualitatively discerned by visual examination

Results

Infarct size study Fig 2 shows the changes in mean HR and AP following coronary occlusion in the four groups of animals used in this study Changes in HR and AP are illustrated only for the first 4 hours following coronary occlusion it is felt that only during this period were these hemodynamic parameters important in influencing infarct size HR in the sham operated dogs was not significantly different from that in the acute controls at the time of coronary occlusion, and it did not differ from that in the acute controls at any time following coronary occlusion ($P > 0.05$) HR in both the chronically denervated and acutely denervated animals was significantly less than that in the acute controls at the time of coronary ligation, and both remained significantly less at all times ($P < 0.05$) AP in the chronically denervated and the sham operated dogs was not significantly different from that in acute controls either at the time of ligation or at any time during the 4 hour period of observation However AP in the acutely denervated animals was significantly less than that in acute controls at the time of ligation and at all intervals following ligation

Table I illustrates an analysis of infarct sizes found in the hearts of these animals In this table P values for infarct sizes in the acutely denervated chronically denervated and sham operated groups represent significance when compared to acute controls Note in Table I that within the acute control animals observed infarct sizes were very consistent and this small dispersion indicates the reproducibility of the method used for infarct size determination Mean infarct size in the acutely denervated dogs was 15 0 per cent of LV weight compared 20 1 per cent in the acute controls The difference was statistically significant However it can be seen that a far greater reduction in infarct size was observed in

a 2 week period[30] However the precise factors which initiate a growth of collaterals are not sufficiently defined to predict their role in the completely denervated heart

Summary

The effect of acute coronary ligation on infarct size was studied in (1) ten acute control dogs which were non denervated (2) in six acutely denervated dogs in which the heart was denervated immediately prior to coronary ligation and in which intra-cardiac reflexes were pharmacologically blocked (3) in seven chronically denervated dogs in which intrapericardial nerves were cut 2 weeks prior to ligation and (4) in four dogs which were sham operated 2 weeks prior to ligation Infarct size was determined using a nitro blue tetrazolium stain for dehydrogenase activity Infarct sizes in acute controls acutely denervated chronically denervated and sham operated hearts were 20 1 15 0 3 8 and 21 0 per cent of left ventricular weight respectively Infarct sizes in acutely and chronically denervated hearts were significantly less than in acute controls ($P < 0.05$) In further studies the fluorescent stain thioflavin S was used to demonstrate that perfusion of myocardium distal to the ligation was substantially greater in chronically denervated hearts than in acute controls

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in the chronically denervated heart is much smaller than that produced in the acutely denervated heart. Possible mechanisms involved in these effects are discussed below.

Acute cardiac denervation with adrenergic blockade. Since selective parasympathectomy or sympathectomy were not performed in the present experiments, it is impossible to state with certainty whether the reduction in infarct size was due to removal of parasympathetic or sympathetic influences. However, because certain earlier studies have indicated that selective sympathectomy results in a reduction in infarct size following acute coronary occlusion,[13-15] because more recent studies have suggested a beneficial effect of beta adrenergic blockade,[1,4,6] and because of evidence indicating that alpha adrenergic constrictor activity may be increased during coronary insufficiency,[10,11] it is felt that the effects observed were due primarily to removal of sympathetic influences.

The reduction in infarct size observed with acute cardiac denervation and adrenergic blockade is quantitatively similar to that observed following beta adrenergic blockade alone when infarct size was determined by the NBT method used here.[1,6] Beta adrenergic blockade is thought to exert its effect by reducing heart rate, and consequently increasing diastolic myocardial perfusion, and by decreasing myocardial oxygen demand.[8] In the present experiments, heart rate in the acutely denervated animals was substantially less than that in acute controls. However, the systemic perfusion pressure in the acutely denervated animals was also less than that in acute controls, and it is difficult to assess the net effect of the reduced heart rate and the reduced perfusion pressure. Nevertheless, it is probable that the reduction in infarct size observed following acute cardiac denervation with adrenergic blockade has largely the same basis as that observed following beta adrenergic blockade alone.

Chronic cardiac denervation. The mechanisms responsible for the dramatic reduction in infarct size seen in the chronically denervated heart are entirely unknown. However, it is apparent that these mechanisms are much more effective than those operative in the acute experiments.

The metabolism of the chronically denervated heart is not well defined, but Gregg and associates[4] have reported that oxygen consumption of the chronically denervated heart is approximately 50 per cent of that in the non denervated heart. The denervation technique used by Gregg and colleagues was different from that used in this study, and oxygen consumption was not measured in the present experiments. But if the finding of Gregg and colleagues can be applied to the chronically denervated animals seen in this study, such a reduced oxygen demand would be expected to maintain viability of myocardium, especially in the borderline regions.

In addition to the possible effects of a reduced oxygen demand, it is apparent from the thioflavin S studies that in the chronically denervated heart there was a substantially improved perfusion of the myocardium distal to the coronary ligation. It has been suggested that mechanical irritation of the epicardial surface promotes an increased vascularity of the epicardium.[29] However, the results obtained in sham operated dogs demonstrate that this effect cannot explain the improved perfusion seen in the chronically denervated hearts. The sham operated animals were subjected to the same epicardial irritation as the chronically denervated animals, but showed no reduction in infarct size following acute coronary occlusion. It appears more likely that the improved collateral perfusion and the reduction in infarct size were due to some chronic effect of sympathectomy. The results obtained from the one incompletely denervated animal in the chronically denervated group add credence to this proposal. Thus, this animal showed no cardiac response to vagal stimulation, no response to left stellate ganglion stimulation, and only a slight response to right stellate ganglion stimulation. But this animal showed a greater quantity of non perfused myocardium than any other animal in the chronically denervated group.

Whether the increased perfusion of myocardium distal to the ligation was due to a removal of constrictor activity from existing collaterals or to a growth of additional collaterals is uncertain. The apparently substantial reduction in non perfused myocardium in conjunction with the difference in infarct size between chronically denervated and acutely denervated hearts with adrenergic blockade may indicate an actual growth of new channels. It is known that a substantial growth of collaterals can occur within

The sıgnıficance of hypotensıon developıng durıng treadmıll exercıse testıng*

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Graded treadmıll exercıse testıng ıs a useful non ınvasıve method of determınıng not only the presence of sıgnıficant coronary artery dısease but also of assessıng the functıonal capacıty of the patıent In addıtıon to the development of horızontal depressıon of the ST segment varıous other parameters such as the blood pressure response[3] arrhythmıas[5,6] and chest paın can be useful ın the over all evaluatıon of an exercıse test A rıse ın systolıc blood pressure durıng exercıse testıng ıs the normal response[7,8] On the other hand a fall ın systolıc pressure durıng exercıse has been suggested as a relıable sıgn of marked left ventrıcular dysfunctıon secondary to crıtıcal coronary artery dısease

This study was undertaken to evaluate the sıgnıficance of exercıse ınduced hypotensıon and to better define the relatıonshıp of the hypotensıve response to the findıngs at cardıac catheterızatıon In order to determıne the underlyıng pathology present ın patıents developıng hypotensıon durıng exercıse testıng we have evaluated the coronary anatomy and restıng left ventrıcular functıon of a group of patıents wıth thıs sıgn In addıtıon to clarıfy further those angıographıc and hemodynamıc findıngs assocıated wıth hypotensıon we have compared these observatıons to a group of patıents wıth normal blood pressure response to exercıse

Methods

The study group was composed of patıents evaluated for chest paın and referred for treadmıll testıng Exercıse tests were performed ın the fastıng state and medıcatıons were dıscontınued for at least 3 days before testıng Nıtroglycerın was wıthheld the day of treadmıll testıng Patıents were exercısed by the protocol of Bruce employıng a modıfied bıpolar V_5 chest lead Exercıse was contınued untıl 90 per cent or more of the predıcted maxımal heart rate was achıeved ıschemıc changes appeared and/or hypotensıon or angına developed Cuff blood pressure was measured over the brachıal artery employıng a sphygmomanometer and recorded standıng at rest durıng the final mınute of each 3 mınute stage and at the onset of angına dızzıness or ST segment depressıon Hypotensıon durıng exercıse testıng was defined as a fall ın systolıc pressure below the restıng level If hypotensıon was confirmed by a second measurement made wıthın 20 seconds the test was stopped An ıschemıc response was defined as horızontal or down slopıng ST segment depressıon of at least 1 mm (10) of 0 08 sec duratıon or greater

Over a two year perıod from July 1974 to June 1976 1 105 patıents underwent treadmıll testıng for suspected coronary artery dısease Thırty patıents exhıbıted hypotensıon durıng the exercıse test comprısıng 2 7 per cent of the total

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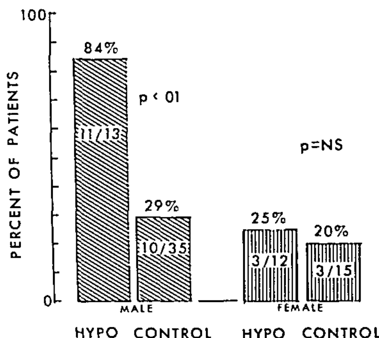


Fig 1 The number of positive exercise tests was significantly higher in hypotensive males compared to control males (84 per cent and 29 per cent) Females had a similar number of positive exercise tests (25 per cent and 20 per cent) *Hypo* = hypotensive group

A positive exercise test was observed in fourteen of the 25 patients in Group I (56 per cent) compared to 13 of the 50 patients in Group II (26%) ($p < 0.02$) When males and females were considered separately it was noted that males accounted for most of the positive exercise tests in both groups 11 of 14 (76 per cent) in Group I and 10 of the 13 (77 per cent) in Group II (Table II) Furthermore the incidence of positive exercise tests was significantly higher in Group I males (11 of 13 tests 84 per cent) when compared to females in the same group (three of 12 tests 25 per cent) or when compared to Group II males (10 of 35 tests 29 per cent) (both $p < 0.01$) (Fig 1) Females in both groups had a similar incidence of positive exercise tests 25 per cent in Group I and 20 per cent in Group II (Fig 1)

Hemodynamic and angiographic correlates The findings at cardiac catheterization are tabulated in Table III Mean left ventricular end diastolic pressures were similar (12 2 vs 11 6 mm Hg) although the control group had a slightly higher frequency of patients with left ventricular end diastolic pressures over 14 mm Hg (26 per cent vs 20 per cent) The mean cardiac index and the percentage of patients with a cardiac index below 2 5 L./min /M^2 was not different in both groups of patients

Although the incidence of coronary artery disease in Group I was 52 per cent (13 of 25 patients) compared to 36 per cent (18 of 50 patients) in the control group this difference was not statistically significant (p = NS) As mentioned above the incidence of positive exercise tests in Group I was 56 per cent of which one was a false positive test In Group II there were three submaximal and two false negative tests Therefore the difference in positive exercise tests between Groups I and II (56 per cent vs 26 per cent) is due to the higher frequency of inadequate and false negative tests in the control group and the presence of one false positive test in the hypotensive group

When males and females were considered separately it was noted that the majority of patients with coronary artery disease were males 10 of 13 patients in Group I and 14 of 18 patients in Group II both 77 per cent It was also apparent that the incidence of significant coronary artery disease was higher among hypotensive males 10 of 13 (77 per cent) when compared to control males 14 of 35 (40 per cent) ($p < 0.01$) (Fig 2) Females had a

Table I. Clinical characteristics

	Group I (25 patients)		Group II (50 patients)	
	Range	Mean	Range	Mean
Sex				
Male	13 (52%)		35 (70%)	
Female	12 (48%)		15 (30%)	
Age (yrs.)	37-62	50.2	25-69	46.8
Resting BP (mm. Hg)				
Systolic	106-170	124.8	94-200	123.7
Diastolic	70-100	78.5	60-105	77.9
Previous MI	6 (24%)		8 (16%)	

BP = blood pressure; MI = myocardial infarction; yrs = years.

Table II. Results of treadmill exercise test

	Group I (25 patients)		Group II (50 patients)	
	Range	Mean	Range	Mean
Duration (sec.)	130-840	420.2	30-840	487.3
FAI (%)	(−20)–(+58)	+13.1	(−20)–(+75)	+8.4
Max. HR	117-175	146.5	95-185	152.5
Change in HR	22-111	59.8	32-89	69.2
Fall in systolic BP (mm. Hg)				
From control	8-50	21	–	–
From peak	20-110	34.8	–	–
ST depression (mm.)	1-5		1-4	
Positive test	14 (11 males)		13 (10 males)	

FAI = functional aerobic impairment; HR = heart rate; BP = blood pressure; Max = maximal.

Table III. Cardiac catheterization findings

	Group I (25 patients)		Group II (50 patients)	
	Range	Mean	Range	Mean
LVEDP (mm. Hg)	3-35	12.2	2-24	11.6
LVEDP > 14	5 (20%)		13 (26%)	
CI (L/min/M²)	1.32-4.80	2.8	1.84-4.43	2.92
CI < 2.5	7 (28%)		12 (24%)	
CAD patients	13 (10 males)		18 (14 males)	
Vessels involved				
1	4		8	
2	4		5	
3	4		5	
LM	1		–	

LVEDP = left ventricular end-diastolic pressure; CI = cardiac index; CAD = coronary artery disease; LM = left main coronary artery.

number of patients exercised. Five of these patients refused further evaluation and were excluded from the study. In the remaining 25 patients, cardiac catheterization was performed within 2 weeks of the exercise test. These 25 patients (Group I) were compared to a group of 50 consecutive unselected patients that underwent exercise testing and had a normal blood pressure response (Group II). Coronary arteriography by the Judkins[11] or Sones and Shirey[1] techniques was performed in all patients in multiple projections using Renograffin 76 per cent. Significant coronary artery disease was defined as obstruction ≥ 75 per cent in one or more of the major vessels.

Statistical significance was determined using the chi square and Student's t test for nonpaired data.

Results

Clinical characteristics. There were 25 patients in Group I and 50 patients in the control group. In Group I there were 13 males (52 per cent) and 12 females (48 per cent) compared to 35 males (70 per cent) and only 15 females (30 per cent) in the control group (P = NS) (Table I). The mean age was comparable: 50.2 years in Group I and 46.8 years in Group II. Mean resting blood pressure was similar in both groups. A history of previous myocardial infarction was comparable in Groups I and II (24 per cent vs 16 per cent).

Treadmill testing correlations. Table II summarizes the results of exercise testing. Patients with hypotension manifested a decrease in mean exercise duration (420 sec. vs 487 sec.) and their mean aerobic capacity was slightly lower (+13.1 per cent vs +8.4 per cent) when compared to the control patients, but these differences were not statistically significant. The mean maximal heart rate and the mean change in rate (from control to maximal) were also similar in both groups of patients. However, only two Group I patients (8 per cent) achieved 90 per cent of their predicted target rate compared to 19 Group II patients (38 per cent) ($p < 0.01$). In those patients developing hypotension, the mean fall in systolic blood pressure was 21 mm. Hg from resting levels and 34.8 mm. Hg from peak pressure achieved during the exercise performance. By definition, no drop in blood pressure was seen among the patients in the control group.

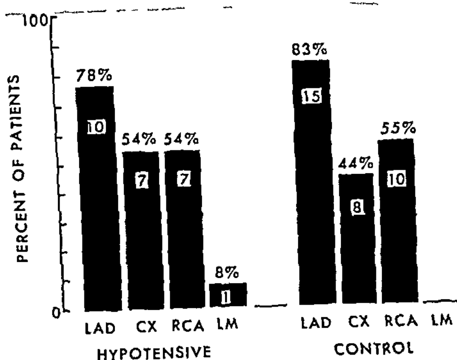


Fig 3 The distribution of vessels with significant obstruction was similar in hypotensive and control groups. The vessel most frequently involved was the left anterior descending coronary artery

portion of the left ventricular mass became ischemic thus producing left ventricular dysfunction However it is difficult to ascertain the severity of coronary artery disease in hypotensive patients unless a group of patients with normal blood pressure response is available for comparison

Although in this study no attempt was made to identify the immediate physiologic mechanisms that led to hypotension we believe it is important to better define the pathologic findings present in hypotensive patients which may contribute to the development of this abnormal response

Clinical characteristics were similar in both groups of patients but it was interesting to note the higher percentage of females in the hypotensive group (Table I) However (nine of 12) 75 per cent of the female patients in this group had normal coronary arteries an incidence similar to the one observed in control females Based on the angiographic findings (see Results section) five of these nine hypotensive patients were considered normal two had mitral valve prolapse without mitral regurgitation and two had findings compatible with a cardiomyopathy All had normal or in one case borderline left ventricular end-diastolic pressures These findings suggest that a hypotensive response in females might not connote coronary artery disease nor severe left ventricular dysfunction This result is in agreement with the findings of Thomson and Kelemen who in their study of 15 patients with coronary artery disease and exercise induced hypotension found only one female

Although the incidence of positive treadmill tests was significantly higher in the hypotensive group the incidence of coronary disease was not different between groups as a whole This apparent discrepancy is clarified if one realizes that there were three submaximal and two false negative tests in the control group and one false positive test in the hypotensive group Of interest was the fact that when males and females were considered separately the incidence of coronary artery disease was higher among males with hypotension compared to control males (77 per cent vs 40 per cent $p < 0.01$) However the results of this study showed no correlation between exercise induced hypotension and the absence or presence of coronary artery disease Moreover the number and distribution of diseased vessels and the severity of involvement

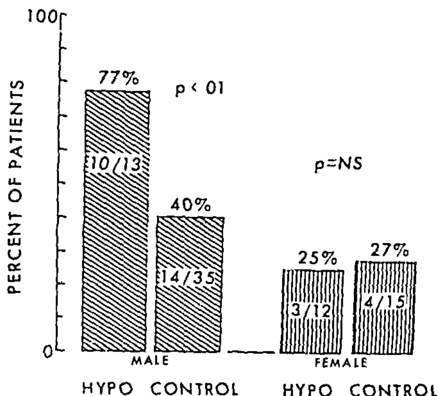


Fig 2 The number of patients with significant coronary artery disease was higher in hypotensive males compared to control males (77 per cent and 40 per cent) Females had a lower but comparable incidence of coronary artery disease (25 per cent and 27 per cent) *Hypo* = hypotensive group

similar incidence of significant coronary disease, 25 per cent in Group I and 27 per cent in Group II (Fig 2) However, no significant differences were noted in the degree of narrowing or number of diseased vessels between groups (Table III) Males accounted for the majority of patients with two vessel disease and for all patients with three vessel disease in both groups In addition, the distribution of coronary lesions showed predominant involvement of the left anterior descending coronary artery in both groups 78 per cent and 83 per cent in Groups I and II respectively, and a similar distribution of left circumflex and right coronary artery narrowing An isolated narrowing of the left main coronary artery was seen in one patient with hypotension (Fig 3)

Nine of the 12 females in Group I (75 per cent) did not have significant coronary artery disease Five of the nine had normal left ventricular end diastolic pressures and normal left ventriculograms Two had normal left ventricular end diastolic pressures, abnormal ventriculograms and mitral valve prolapse without mitral regurgitation Two had abnormal ventriculograms one with a left ventricular end diastolic pressure and 15 mm Hg and the other with normal pressures

Three of the 13 males in Group I (23 per cent) were free of significant coronary artery disease All three had normal left ventricular end diastolic pressures two with abnormal and one with normal left ventriculograms

Discussion

The role of exercise testing as a non invasive diagnostic tool in patients with suspected coronary artery disease is well established Constant monitoring of physiologic parameters during the exercise performance is important not only for reasons of safety, but for the opportunity to detect abnormal responses One such abnormal response to exercise is a drop in systolic blood pressure However the significance of exercise induced hypotension in patients evaluated for chest pain and its value as a predictor of coronary artery disease remains to be determined

Exercise induced hypotension has been reported as a reliable sign of severe coronary artery disease[4] Thomson and Kelemen[4] described 15 patients with hypotension accompanying the onset of angina and postulated that critical coronary artery narrowing caused the systolic pressure to fall because during exercise a large

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did not differ between groups Equally striking was the similarity in the resting mean end diastolic pressure and cardiac index between groups and the comparable number of patients with wall motion abnormalities

The hypotensive response to exercise may not imply left ventricular dysfunction potentially secondary to ischemia Hypotension can occur in normal subjects during maximal exhaustive exercise This is accepted as a normal event since it occurs when subjects enter an anaerobic phase of exercise However, only two of the patients in the hypotensive group reached 90 per cent of their predicted maximal heart rate and these rates were attained at low levels of exercise Since heart rate and anaerobic metabolism do not appear to be the determinants in the hypotensive responses that were observed other variables must be playing a role Vasovagal responses can be responsible for exercise induced hypotension, but in this case hypotension occurs in the post exercise period and is associated with bradycardia None of our patients demonstrated this type of response The major determinants of blood pressure during exercise include heart rate myocardial contractility and the response of the peripheral vascular system, especially to circulating catecholamines[7] A primary impairment of the autonomic system appears unlikely, since none of our patients developed orthostatic hypotension The pressure changes during exercise are an index of the inotropic reserve of the left ventricle[13] However, since peripheral vascular resistence diminishes markedly during upright exercise the change in pressure underestimates the inotropic reserve of the ventricle[13]

Clinical implications

From our data, we conclude that among patients evaluated for chest pain who develop hypotension during an exercise test, coronary artery disease is not the usual underlying pathology in females Males on the other hand have a higher incidence of coronary artery disease However the extent and distribution of their disease appears to be no different from that of patients without hypotension It should be reiterated that the purpose of this study was to clarify the underlying pathology present in patients with hypotension, and no attempt was made to identify the physiologic mechanisms that led to this abnormal response Further studies with hemodynamic monitoring during exercise testing are warranted

Summary

The significance of hypotension developing during treadmill exercise testing was evaluated and correlated with the findings at cardiac catheterization in two groups of patients Twenty five patients (Group I) had a fall in systolic pressure during exercise and were compared to 50 consecutive unselected patients (Group II) with a normal blood pressure response Clinical characteristics were similar in both groups Females comprised 48 per cent of the patients in Group I and only 30 per cent in Group II The incidence of significant coronary artery disease was not different when the two groups were compared as a whole 56 per cent in Group I and 36 per cent in Group II (P = NS) When males and females were considered separately, it was noted that the incidence of coronary artery disease was higher in hypotensive males (77 per cent) when compared to control males (40 per cent) ($p < 0.01$) Females in both groups had a lower but comparable incidence of coronary artery disease (25 per cent and 27 per cent, respectively) Resting hemodynamics and angiographic characteristics such as contraction abnormalities and the number and distribution of diseased coronary vessels, were similar in both groups of patients These findings suggest that hypotension in females does not necessarily connote coronary artery disease Males with hypotension have a higher incidence of coronary artery disease, but the extent and distribution of their disease is no different from that of patients with a normal blood pressure response to exercise

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Table I Mean carboxyhemoglobin levels in the control periods before and after breathing CO and before and after breathing compressed purified air and mean ventricular fibrillation threshold (VFT) in the control periods after breathing CO and after breathing compressed purified air

	Control	*Before CO*	*After CO*	*Control*	*Before compressed purified air*	*After compressed purified air*
Mean carboxyhemoglobin level ± 1 standard deviation (%)	1 08 ± 0 36	1 11 ± 0 34	6 34 ± 0 53	1 16 ± 0 34	1.18 ± 0 37	1 07 ± 0 38
Mean ventricular fibrillation threshold ± 1 standard deviation (milliamperes)	12.8 ± 6 8		8 1 ± 3 8	11 2 ± 6 0		15 0 ± 5 1

with a 182 Co Oximeter The ventricular fibrillation threshold was then determined

The amplified ECG potentials from the Grass recorder were fed into a triggering circuit whose output was coupled to an opto isolator The output from the opto-isolator was connected to a constant current stimulator The output of the stimulator was connected to a bipolar electrode constructed of two silver tabs 5 mm in diameter each with a 4 cm separation

The electrodes of the stimulator were placed over the same region of myocardial injury during each moment of stimulation Test shocks were applied to the vulnerable period and were delivered every 10 seconds for 30 msec A shock of given amplitude was repeated three times before the current was increased at increments of 1 milliampere until ventricular fibrillation ensued The current just adequate to provoke ventricular fibrillation was interpreted as the ventricular fibrillation threshold After ventricular fibrillation occurred this was treated by defibrillation A 30 minute waiting period next ensued

Blood was then taken from the femoral artery and analyzed for carboxyhemoglobin and hemoglobin After this the dogs breathed from a tank in a randomized blind study either 100 p p m of CO for 2 hours or compressed purified air for 2 hours Eleven dogs were randomized to CO inhalation and 10 dogs to compressed purified air inhalation

Two hours after either CO or compressed, purified air was breathed femoral arterial blood was drawn and analyzed for carboxyhemoglobin and hemoglobin The ventricular fibrillation threshold was then again determined

Results

One of 21 dogs (5 per cent) developed spontaneous ventricular fibrillation 100 minutes after breathing CO

Table I indicates the mean arterial carboxyhemoglobin level ± 1 standard deviation in the control periods before and after breathing CO and before and after breathing compressed purified air The mean arterial carboxyhemoglobin level significantly increased after CO inhalation ($t = 31\ 26$ $P < 0\ 001$) and significantly decreased after compressed purified air ($t = 2\ 70$ $P < 0\ 025$)

Table I also shows the mean ventricular fibrillation threshold ± 1 standard deviation in the control periods after breathing CO and after breathing compressed purified air In comparison to breathing compressed purified air CO inhalation caused a significant decrease in ventricular fibrillation threshold ($t = 4\ 25$ $P < 0\ 001$)

Discussion

The increased ventricular fibrillation threshold after breathing compressed purified air may be attributed to increased electrical stability of the injured myocardium 3 hours 20 minutes after acute myocardial injury compared to 30 minutes after acute myocardial injury The decreased ventricular fibrillation threshold after breathing sufficient CO to raise the mean arterial carboxyhemoglobin level to 6 34 per cent may be attributed to increased myocardial ischemia lowering the ventricular fibrillation threshold Extension of the area of myocardial injury by the increased hypoxia after CO and depression of myocardial contractility by the CO[7] may also

Carbon monoxide and ventricular fibrillation threshold in dogs with acute myocardial injury*

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Exposure of carbon monoxide (CO) in concentrations found during heavy atmospheric CO pollution impairs cardiovascular function in patients with cardiovascular disease[1-7] or in normal subjects[8-10] Cohen and associates also found an association between atmospheric CO pollution in Los Angeles and case fatality rates in patients with acute myocardial infarction admitted to 35 Los Angeles hospitals

DeBias and associates[12] showed that in monkeys with experimental myocardial infarction a greater degree of myocardial ischemia occurred in monkeys exposed to 100 p p m of CO than in those breathing room air DeBias[13] also measured the ventricular fibrillation threshold in five monkeys with experimental myocardial infarction who breathed 100 p p m of CO for 6 hours and in four monkeys with experimental myocardial infarction who breathed ambient air DeBias observed[13] that CO inhalation to raise the mean arterial carboxyhemoglobin level to 10 2 ± 1 8 per cent was a significant factor in enhancing ventricular fibrillation in monkeys with acute myocardial infarction

We investigated the effect of breathing in a blind randomized study either 100 p p m of CO or compressed purified air for 2 hours on ventricular fibrillation threshold in 21 dogs with experimental acute myocardial injury The data from this study are presented in this report

Methods

Dogs were anesthetized with intravenous pentobarbital 45 mg /Kg and connected through an endotracheal tube with a volume controlled Harvard Pump Respirator Catheters were inserted into the right femoral artery and vein Lead II of an electrocardiogram (ECG) and the right femoral arterial pressure were recorded on a Grass Model 7 Polygraph recorder

Experimental acute myocardial injury was induced in the dogs by ligation of the left anterior descending coronary artery just distal to the first diagonal branch[14] An ECG verified the presence of acute myocardial injury in all dogs The area of myocardial injury demonstrated bluish discoloration and paradoxical motion in all dogs After a 30 minute wait, the following protocol was performed in 21 surviving dogs

Blood was drawn from the femoral artery and analyzed for carboxyhemoglobin and hemoglobin

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...vein coronary artery bypass graft ...great success in the symptomatic ... of angina pectoris Postoperative ... es have demonstrated that the ... rate is approximately 80 to 90 per ... the first year[1] Graft occlusion ...ops at the graft to coronary artery ...site and is due to technical failures ... of the intrinsic coronary artery ... coronary artery dissection[4] This ...bes an unusual form of saphenous ...clusion due to a postoperative bacte...

...tient was in good health until four years ... when he suffered an acute anterolateral ...rction complicated by ventricular fibrillation. ...he did well, however except for mild exertional ...eeks before death he developed unstable angina ...few attacks of rest pain and was admitted to ...pkins Hospital. Pertinent physical findings on ...ed a blood pressure of 110/70 mm. Hg., clear ...rade 2/6 systolic ejection precordial murmur ...p. Chest radiograph showed a normal-sized ...ardiogram, new ST depression in Leads, 2, 3, ...at increased during worsening pain. Cardia...

...n unstable condition, cardiac catheterization was performed and showed a left ventricular (LV) pressure of 118/0-8 mm. Hg. with an LV end-diastolic pressure that rose to 18 mm. Hg after contrast, and a right ventricular (RV) pressure of ... mm. Hg. Coronary arteriography showed a 70 to 90 per cent narrowing of the proximal left anterior descending coronary artery total obstruction of the left circumflex, and a > 90 per cent proximal narrowing of the right coronary artery with multiple distal narrowings. Left ventriculogram showed good over-all LV contractility. Ejection fraction calculated at 62 per cent. Because of persistent rest pain without enzyme changes he underwent a saphenous vein coronary artery bypass operation. A saphenous vein bypass was placed in his left anterior descending coronary artery but exploration of the right coronary artery showed it to be unsatisfactory for bypass. Methicillin in doses of 2 grams per day was administered 24 hours before surgery and was continued for 5 days afterwards.

Postoperatively the patient developed respiratory difficulties, gastrointestinal bleeding and a mediastinal wound infection with *Pseudomonas aeruginosa*. Despite surgical débridement and appropriate antibiotic therapy with adequate blood levels of gentamycin tested against his organism in vitro he continued to do poorly, with spiking fevers, hypotension and bleeding from his mediastinal wound, and he died three weeks after the initial operation.

At autopsy the mediastinum was open. Grossly purulent material and extensive organizing fibrinous adhesions were present in the anterior mediastinum and adjacent pericardium. The heart weighed 490 grams and a purulent pericarditis involved its anterior surface. The pericardial sac contained 100 ml. of bloody fluid loculated posteriorly. The saphenous vein bypass graft to the distal left anterior descending coronary artery was also covered by shaggy adhesions. Postmortem coronary arteriography of the graft and intrinsic coronary arteries demonstrated total occlusion of the vein graft (Fig. 1). Only the first few millimeters of the distal portion of the anastomosis filled retrogradely through the left anterior descending coronary artery. The native coronary arteries had >75 per cent proximal narrowings of the left anterior descending and right coronary arteries, and total occlusion of the left circumflex coronary arteries b... atheroslerotic plaque. The myocardium was hypertrophied with a wall thickness of up to 1.8 cm. A transmural scar was present

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have contributed to the decreased ventricular fibrillation threshold after CO inhalation

The data from this blind randomized study are of public health importance as the concentration of CO used may be encountered with heavy atmospheric CO pollution (peak freeway traffic) or with smoking The data are also compatible with the increased incidence of sudden death in patients with coronary heart disease who are heavy cigarette smokers [15]

Summary

In a blind, randomized study, the effect of breathing 100 p p m of CO versus compressed, purified air for 2 hours on ventricular fibrillation threshold (VFT) was investigated in 21 dogs with acute myocardial injury The mean arterial carboxyhemoglobin was 1 16 per cent in the air control period, 1 07 per cent after air 1 08 per cent in the CO control period, and 6 34 per cent after CO In comparison to air CO increased the mean arterial carboxyhemoglobin ($P < 0\,001$) One dog developed spontaneous ventricular fibrillation 100 minutes after CO Mean VFTs in the other 20 dogs were $12\,8 \pm 6\,8$ milliamperes in the CO control period, $8\,1 \pm 3\,8$ milliamperes after CO, $11\,2 \pm 6\,0$ milliamperes in the air control period, and $15\,0 \pm 5\,1$ milliamperes after air In comparison to air, CO decreased the VFT ($P < 0\,001$) These data show that breathing 100 p p m of CO for 2 hours reduces the VFT in dogs with acute myocardial injury

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Case reports

Acute postoperative graft phlebitis A rare cause of saphenous vein–coronary artery bypass failure

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Grover M Hutchins, M D
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Saphenous vein coronary artery bypass graft surgery has had great success in the symptomatic treatment of angina pectoris Postoperative angiographic studies have demonstrated that the graft patency rate is approximately 80 to 90 per cent within the first year[1] Graft occlusion usually develops at the graft to coronary artery anastomosis site and is due to technical failures compression of the intrinsic coronary artery thrombosis or coronary artery dissection[2-4] This report describes an unusual form of saphenous vein graft occlusion due to a postoperative bacterial phlebitis

Case report

A 6 year-old male was in good health until four years before his death when he suffered an acute anterolateral myocardial infarction complicated by ventricular fibrillation Subsequently he did well, however except for mild exertional angina Four weeks before death he developed unstable angina with multiple daily attacks of rest pain and was admitted to The Johns Hopkins Hospital. Pertinent physical findings on admission included a blood pressure of 110/70 mm Hg clear lung fields, a Grade 2/6 systolic ejection precordial murmur and an S gallop Chest radiograph showed a normal sized heart and electrocardiogram new ST depression in Leads 2, 3 F V to V that increased during worsening pain Cardiac enzymes were normal.

Because of his unstable condition cardiac catheterization was performed and showed a left ventricular (LV) pressure of 118/0-8 mm. Hg with an LV end-diastolic pressure that rose to 18 mm. Hg after contrast and a right ventricular (RV) pressure of 25/0-5 mm. Hg Coronary arteriography showed a 70 to 90 per cent narrowing of the proximal left anterior descending coronary artery total obstruction of the left circumflex and a > 90 per cent proximal narrowing of the right coronary artery with multiple distal narrowings. Left ventriculogram showed good over all LV contractility Ejection fraction calculated at 68 per cent Because of persistent rest pain without enzyme changes, he underwent a saphenous vein coronary artery bypass operation A saphenous vein bypass was placed in his left anterior descending coronary artery but exploration of the right coronary artery showed it to be unsatisfactory for bypass Methicillin in doses of 2 grams per day was administered 24 hours before surgery and was continued for 5 days afterwards

Postoperatively the patient developed respiratory difficulties, gastrointestinal bleeding and a mediastinal wound infection with *Pseudomonas aeruginosa* Despite surgical débridement and appropriate antibiotic therapy with adequate blood levels of gentamycin tested against his organism in vitro he continued to do poorly with spiking fevers hypotension and bleeding from his mediastinal wound and he died three weeks after the initial operation

At autopsy the mediastinum was open Grossly purulent material and extensive organizing fibrinous adhesions were present in the anterior mediastinum and adjacent pericardium. The heart weighed 490 grams, and a purulent pericarditis involved its anterior surface The pericardial sac contained 100 ml. of bloody fluid loculated posteriorly The saphenous vein bypass graft to the distal left anterior descending coronary artery was also covered by shaggy adhesions Postmortem coronary arteriography of the graft and intrinsic coronary arteries demonstrated total occlusion of the vein graft (Fig 1) Only the first few millimeters of the distal portion of the anastomosis filled retrogradely through the left anterior descending coronary artery The native coronary arteries had >75 per cent proximal narrowings of the left anterior descending and right coronary arteries, and total occlusion of the left circumflex coronary arteries by atherosclerotic plaque The myocardium was hypertrophied with a wall thickness of up to 1 6 cm A transmural scar was present

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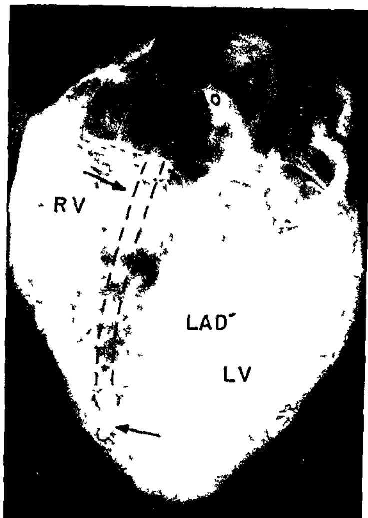


Fig 1 Postmortem coronary arteriogram showing course of occluded saphenous vein graft (*dotted lines*) Only the terminal portion of the graft at the anastomosis of the saphenous vein graft to the left anterior descending (*LAD*) coronary artery (*lower arrow*) contains infection mass The intramural abscess is located at upper arrow *Ao* = aorta *LA* = left atrium *LV* = left ventricle *RA* = right atrium *RV* = right ventricle

in the apical inferior left ventricular myocardium and foci of fibrosis were present in the posterior wall Histologic examination of the myocardium demonstrated focal areas of organizing contraction band necrosis indicative of reperfusion of transiently unperfused myocardium but no areas of recent coagulation necrosis

Serial histologic sectioning of the graft to artery anastomosis site demonstrated a widely patent anastomosis (Fig 2) and as suggested from gross examination and postmortem angiography within approximately a few millimeters of the anastomosis an occlusive organizing thrombus was present in the vein graft At the junction of proximal and middle thirds of the graft the wall of the vein was focally necrotic and infiltrated with polymorphonuclear leukocytes (Fig 3) The intramural abscess appeared to be the origin of the thrombus which occluded almost all of the graft Overlying the vein graft was an organizing purulent epicarditis The portion of the vein immediately adjacent to the coronary artery anastomosis was free of thrombus and was not infected The proximal (aorta to vein) anastomosis was intact.

Discussion

This 67 year old man with unstable angina died three weeks after operation of bleeding and sepsis related to a Pseudomonas mediastinitis An unexpected and previously unreported finding at autopsy was thrombosis of a coronary artery saphenous vein bypass graft due to graft phlebitis Although late occlusions may result from fibrous intimal proliferation,[9, 10] most early graft occlusions are related to technical problems at the anastomosis site including anastomoses into vessels of too small a caliber, or ones with distal disease and poor runoff Thrombosis of the graft is frequently associated with thrombosis of the intrinsic coronary artery at the site of anastomosis[6] In this patient, however, early graft failure occurred in the presence of a widely patent technically good anastomosis and thrombosis of the graft did not progress to thrombosis of the grafted coronary artery Thus, although the possible benefit intended from the bypass graft was not obtained without a new intrinsic coronary occlusion or narrowing, his myocardial coronary perfusion was not worsened by the graft failure Consistent with this, at autopsy there was no evidence of a myocardial infarction related to the graft failure

Isolated graft occlusion in this patient was related to graft infection The organizing thrombus arose from a severe acute phlebitis with a mural abscess in the vein graft Although coronary artery bypass operations involve a limb dissection and a fair amount of manipulation of tissue prior to implantation graft infection is a virtually unheard of complication of this procedure The phlebitis in the patient studied here was associated with a severe purulent mediastinitis and pericarditis It is most likely that mediastinitis led to pericarditis and subsequently phlebitis That an infected vein graft might have lead to an overlying purulent pericarditis and mediastinitis is also possible Mediastinitis has been associated with prosthetic valve endocarditis and in some instances which infected site was the initiator of infection is not clear[11]

Although mediastinitis is not an infrequent postoperative complication purulent mediastinitis and even purulent pericarditis are not necessarily associated with graft phlebitis We have studied one other patient with purulent pericarditis after a double coronary artery bypass graft

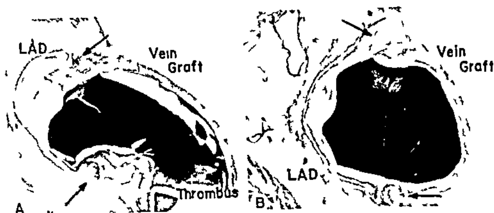


Fig 2 A and B Selected serial histologic sections of the saphenous vein graft to left anterior descending (*LAD*) anastomosis (*lower arrow* in *Fig 1*) *A* Through the graft and opened artery showing end of thrombus in the vein graft and dark staining infection mass in terminal graft and artery The suture line is at the arrows and an atheroma is within the artery but the anastomosis is widely patent *B* Distal to *A* showing the open artery (*below*) roofed by vein graft (*above*) The arrows show the suture line (Both Verhoeff van Gieson stain original magnification ×15)

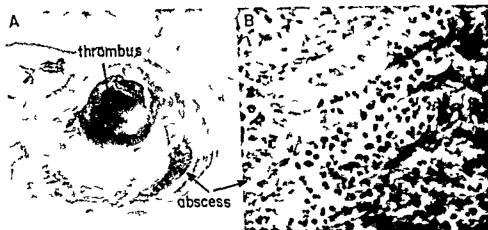


Fig 3 A and B *A* Transverse section of vein graft at the upper arrow of *Fig 1* showing thrombotic occlusion of the lumen related to an intramural abscess (Hematoxylin and eosin stain original magnification ×15) *B* Margin of abscess shown in *A* demonstrating purulent exudate (Hematoxylin and eosin stain original magnification ×450)

operation and neither of his grafts became infected Nevertheless the mediastinal and pericardial infection of this patient who failed to respond to standard therapy may have been a clue to the infectious involvement of the implanted graft Particularly in the setting of a completely thrombosed vessel it is probable that eradication of infection would have required removal of the infected vein

Cardiac infection after heart operations are not common but when they occur the consequences are devastating and generally successful outcome requires prompt surgical intervention It is important to recognize therefore that saphenous vein grafts like prosthetic valves and septal defect patches can become infected and that such infection may be a cause of thrombosis and occlusion

Summary

Most graft occlusions occurring early after saphenous vein coronary artery bypass procedures result from technical problems at the graft to coronary artery anastomosis site This report describes an unusual cause of graft occlusion in a 67 year old man who died three weeks

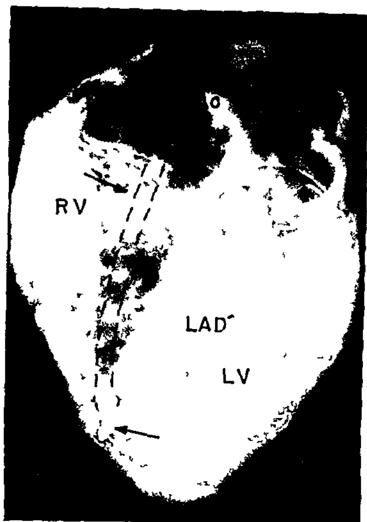


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Although mediastinitis is not an infrequent postoperative complication purulent mediastinitis and even purulent pericarditis are not necessarily associated with graft phlebitis We have studied one other patient with purulent pericarditis after a double coronary artery bypass graft

Simulated tricuspid valve echoes in tricuspid atresia

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Maurice Payot M D *
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Echocardiography is most valuable in the assessment of neonates with hypoplastic right heart complexes While a tricuspid valve echo is usually present in hypoplastic right heart complexes associated with pulmonary atresia the absence of this echo strongly favors tricuspid atresia This communication documents a case of tricuspid atresia proven by catheterization and necropsy in which the echocardiogram showed echoes strongly resembling those of a tricuspid valve

Case report

This two-day-old male infant weighed 3 8 kilograms at birth Cyanosis tachypnea and a heart murmur were detected shortly after birth Umbilical arterial blood gas analyses showed a PO of 38 torr a PCO of 21 torr and a pH of 7 38 while breathing room air while breathing 100 per cent oxygen the PO rose to 52 torr He subsequently developed signs of poor perfusion and acidosis and was transferred to our institution for further evaluation

Physical examination showed a full term baby with tachypnea, mild hyperpnea, central cyanosis and decreased peripheral perfusion The peripheral pulses were barely palpable in all extremities The heart rate was 180 beats/minute the respiratory rate 100/minute The descending aorta blood pressure measured by an umbilical arterial catheter was 60 40 (mean 48) mm Hg A diffuse precordial impulse was felt The first heart sound was normal and the second sound single There was a Grade ⅗ short systolic ejection murmur which was loudest at the mid left sternal border The liver edge was palpated 5 cm below the right costal margin and the spleen tip was 2 cm below the left costal margin Umbilical arterial blood gas analysis showed a pH of 6 99 a PCO of 29 torr and a PO of 64 torr An electrocardiogram showed sinus tachycardia a mean frontal plane QRS axis of +60 degrees and decreased right ventricular forces A chest roentgenogram showed moderate cardiomegaly with normal pulmonary vascular markings

The clinical impression was that the child had a cardiac anomaly resulting in cyanosis and obstruction to left ventricular outflow The diagnoses considered most likely were transposition of the great arteries with tricuspid atresia and a restrictive ventricular septal defect or transposition with a hypoplastic right ventricle

An echocardiogram was obtained from the standard positions (see Figs 1 2 and 3) Fig 1 demonstrates an M Mode sweep from the valve of the posterior great artery through the posterior atrioventricular valve The anterior wall of the posterior great artery was continuous with the ventricular septum and the artery's posterior wall was continuous with the anterior leaflet of the mitral valve The latter lay posteriorly and leftward These findings were consistent with a ventricular d loop On pivoting the transducer cranial and rightward a smaller arterial root (aorta) was identified The valve leaflets of this artery were poorly defined and the arterial root lay anterior to the valve of the larger more posterior great artery The interrelationship of the arterial roots was typical for d transposition (see Fig 2) During the study 2 1 atrioventricular block developed however the atrial contraction that occurred early in diastole had no perceptible effect on the mitral valve motion (Fig 3a) On pointing the transducer to the region of the tricuspid valve an echo pattern was seen that was interpreted as tricuspid valvular in origin (Fig 3b) Although the apparent valve motion was of a lesser amplitude than that of the mitral valve the timing of the "E and "A points was similar to that of the mitral valve echo These echocardiographic patterns could only be recorded during the latter part of the study when 2 1 atrioventricular block was present The echocardiogram was interpreted as being compatible with transposition of the great arteries with a diminutive right ventricle and hypoplastic ascending aorta We thought that we had excluded tricuspid atresia because of the recording of echoes emanating from a structure which appeared to be a tricuspid valve Cardiac catheterization was performed and demonstrated d transposition of the great arteries, tricuspid atresia a diminutive right ventricle a restrictive ventricular septal defect and interrup-

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after operation—a postoperative acute phlebitis of an implanted saphenous vein graft Infection in the graft wall resulted in isolated graft thrombosis in the setting of a patent anastomosis Graft phlebitis in this patient was associated with a purulent pericarditis and mediastinitis which failed to respond to surgical débridement and antibiotic therapy Although mediastinitis is not infrequent, infection of an implanted saphenous *vein coronary artery bypass graft in association* with mediastinitis has never been reported The findings in our case show that such graft infection may occur and may result in graft thrombosis and occlusion

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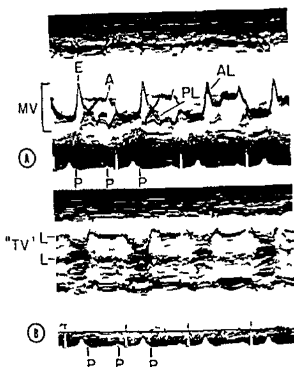


Fig 3 A and B *A Top panel shows* the mitral valve with anterior leaflet and posterior leaflet within a large ventricular chamber The E and A points are shown on the mitral valve *AL* anterior leaflet *MV* mitral valve *PL* posterior leaflet *B* The bottom panel demonstrates the spurious echo located in the usual area of the tricuspid valve which mimics the tricuspid valve with anterior and posterior leaflets Note 2 1 atrioventricular block with a ventriculophasic response is present in these two panels The paper speed (50 mm /sec) is the same as the other examples *L* leaflets *TV* tricuspid valve

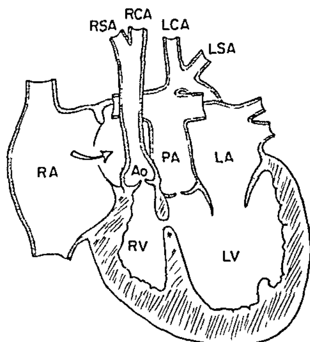


Fig 4 Pathological diagram of the patient showing tricuspid atresia ventricular septal defect and diminutive right ventricle tran position and a hypoplastic aorta an interrupted aortic arch between the innominate and right carotid arteries and a patent ductus arteriosus. *The arrow* indicates the direction of flow through the interatrial communication *Ao* aorta *LA* left atrium *LCA* left carotid artery *LSA* left subclavian artery *LV* left ventricle *PA* pulmonary artery *RA* right atrium *RCA* right carotid artery *RSA* right subclavian artery *RV* right ventricle

small tricuspid valve was present Initially the motion of this echo was judged typical for an anterior atrioventricular valve including the appearance of two leaflets and seemed to satisfy all the criteria established for echoes of tricuspid valve origin The pattern of leaflet motion was similar to that recorded for the mitral valve during second degree atrioventricular block

As no tricuspid valve was present an alternate explanation for the apparent tricuspid echoes was sought There are two reasons to suggest that the diastolic echo motion was the result of atrial contractions Firstly the diastolic motion cannot be explained by ventricular free wall ventricular septal or semilunar valve motion On reviewing the pathological specimen it was unlikely that the echoes could have originated from the right ventricle as this was minute and the distance between the walls was much less than the space between the apparent anterior and posterior echoes of the tricuspid leaflets Secondly the temporal relationship of the echo motion to the electrocardiographic P waves is evident that is the apparent E and A points occur immediately after the P waves That two atrial contractions should result in an apparent E as well as A excursion is undoubtedly the result of 2 1 atrioventricular block Similarly the difference in amplitude of the E and A points is probably related to their timing in relation to the ventricular systole

In tricuspid atresia with a large interatrial communication such as was present in this case the amplitude of the right atrial contraction would be influenced by left ventricular events The difference in amplitude between the apparent E and A points may reflect differences at the beginning and the end of ventricular diastole

In order to determine which atrial structures might have produced the echo pattern the necropsy specimen (Figs 5*a* and 5*b*) was examined in situ The most anterior structure encoun

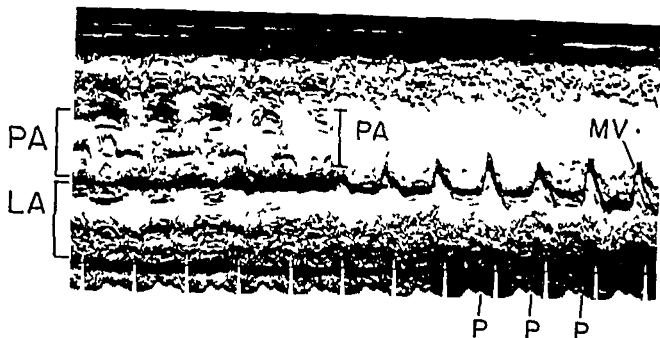


Fig 1 Echocardiogram showing a sweep from the posterior great vessel (the pulmonary artery) through the left ventricle The left artium identified behind the pulmonary root The posterior pulmonary root is continuous with the mitral valve The P waves on ECG are indicated on three of the latter complexes *LA* left atrium *MV* mitral valve *PA* pulmonary artery

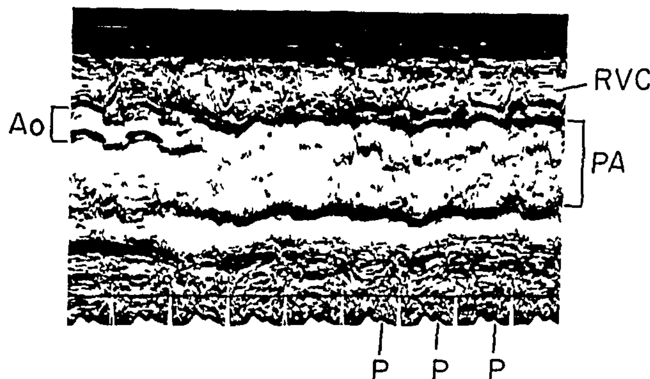


Fig 2 Echocardiogram demonstrating a sweep from the right to the left sides of the patient A small anteroposed aorta is anterior and to the right of the pulmonary artery *On the right hand side of the figure* is the right ventricular cavity The P waves on the ECG are indicated *Ao* aorta *RVC* right ventricular cavity

tion of the aortic arch between the origin of the carotid arteries. No surgical intervention was attempted and the baby subsequently died Necropsy confirmed the diagnoses demonstrated by cardiac catheterization (Figs 4 and 5)

Discussion

Echocardiography has been helpful in identifying various forms of hypoplastic right heart complexes [1-4] The absence of specific echoes from the tricuspid valve leaflets in the presence of a small anterior and rightward ventricle is typical of tricuspid atresia In contrast the presence of a *small amplitude tricuspid echo is usually associated with hypoplastic right ventricle and a* small tricuspid valve Although the clinical findings in this case strongly favored tricuspid atresia the echocardiographic demonstration of apparent tricuspid leaflet motion led us to conclude that a

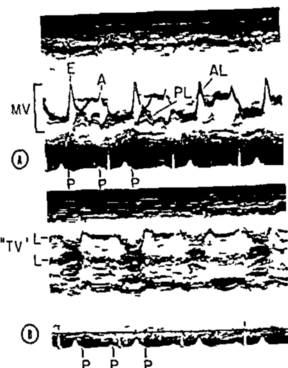


Fig 3 A and B *A Top panel shows* the mitral valve with anterior leaflet and posterior leaflet within a large ventricular chamber The E and A points are shown on the mitral valve *AL* anterior leaflet *MV* mitral valve *PL* posterior leaflet *B* The bottom panel demonstrates the spurious echo located in the usual area of the tricuspid valve which mimics the tricuspid valve with anterior and posterior leaflets Note 2 1 atrioventricular block with a ventriculophasic response is present in these two panels The paper speed (50 mm /sec) is the same as the other examples *L* leaflets *TV* tricuspid valve

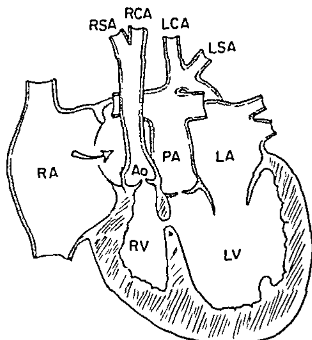


Fig 4 Pathological diagram of the patient showing tricupid atresia ventricular septal defect and diminutive right ventricle transposition and a hypoplastic aorta an interrupted aortic arch between the innominate and right carotid arteries and a patent ductus arteriosus *The arrow* indicates the direction of flow through the interatrial communication *Ao* aorta *LA* left atrium *LCA* left carotid artery *LSA* left subclavian artery *LV* left ventricle *PA* pulmonary artery *RA* right atrium *RCA* right carotid artery *RSA* right subclavian artery *RV* right ventricle

small tricuspid valve was present Initially the motion of this echo was judged typical for an anterior atrioventricular valve including the appearance of two leaflets and seemed to satisfy all the criteria established for echoes of tricuspid valve origin [13] The pattern of leaflet motion was similar to that recorded for the mitral valve during second degree atrioventricular block

As no tricuspid valve was present an alternate explanation for the apparent tricuspid echoes was sought There are two reasons to suggest that the diastolic echo motion was the result of atrial contractions Firstly the diastolic motion cannot be explained by ventricular free wall ventricular septal or semilunar valve motion On reviewing the pathological specimen it was unlikely that the echoes could have originated from the right ventricle as this was minute and the distance between the walls was much less than the space between the apparent anterior and posterior echoes of the tricuspid leaflets Secondly the temporal relationship of the echo motion to the electrocardiographic P waves is evident that is the apparent E and A points occur immediately after the P waves That two atrial contractions should result in an apparent E as well as A excursion is undoubtedly the result of 2 1 atrioventricular block Similarly the difference in amplitude of the E and A points is probably related to their timing in relation to the ventricular systole

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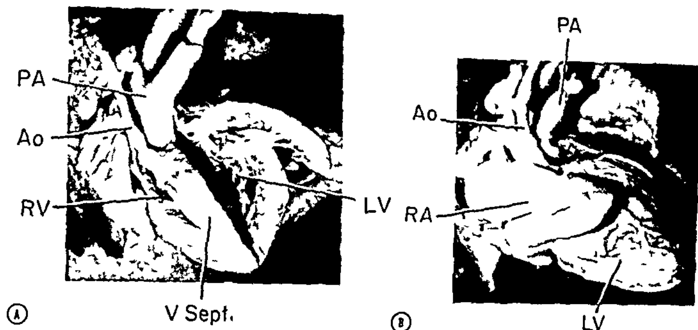


Fig 5 *A* and *B* are photographs of this pathological specimen *A (left panel)* shows the specimen viewed from the front as it lay in the chest *B (right panel)* is the dissected specimen A stick ⅛ inch in diameter just passed through the ventricular septal defect *Ao* aorta *PA* pulmonary artery *RA* right atrium *RV* right ventricle *V Sept* ventricular septum

tered by the echo beam was probably the right atrial appendage It lay interposed between the chest wall and the left ventricle and consequently may have been partially responsible for the apparent tricuspid echo it was however, unlikely to be the sole source of both apparent leaflet motions Normally the space behind the anterior chest wall is occupied by the anterior cardiac structures a space being noted only in the presence of pericardial effusion As no effusion was present the echo which resembles the anterior tricuspid valve leaflet could not have originated from the anterior wall of the right atrial appendage Probably the apparent anterior leaflet echo arose from the posterior wall of the right atrial appendage and the echo resembling the posterior tricuspid leaflet arose from the inferior or posterior wall of the right atrium or the atrial septum Alternatively, both the apparent tricuspid valve leaflet echoes may have originated from the anterior and posterior aspects of the floor of the right atrium

The structural relationships at necropsy were such that it is unlikely that the echoes arose from the interatrial septum or the valve of the foramen ovale Each was too posterior to have resulted in the apparent tricuspid echoes It is conceivable that the valve of the inferior vena cava or the coronary sinus might produce similar echo wave forms however, at necropsy both these structures were too small to have produced the recorded amplitude of motion

Although we have advanced possible explanations for the echocardiographic findings it is possible that none of these are correct Indocyanine green studies at the time of catheterization[17, 18] might have proven useful in further defining the location of the echo but the patient s critical condition precluded such a study For the same reasons, cross sectional echocardiography was not performed

In hypoplastic right heart complexes it is frequently difficult to identify tricupsid valve echoes and, if found the tricuspid valve echo pattern may be quite atypical Fig 6 illustrates such a case The patient had a hypoplastic right ventricle and a small tricuspid valve The echo pattern is less typical of tricuspid valve than the apparent tricuspid echoes from our patient with tricuspid atresia The occurrence of 2 1 atrioventricular block probably led to this rare echocardiographic pattern as during the rest of the examination sinus rhythm was present

Caution should be exercised in identifying tricuspid valve echoes in patients with hypoplastic right ventricle Clearly failure to demonstrate a structure by echocardiography may be the result of absence of that structure or it may

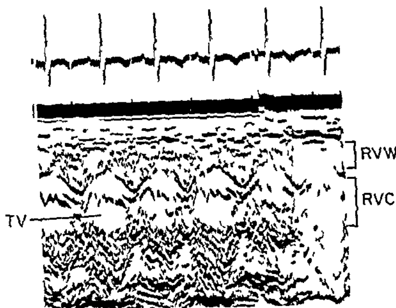


Fig 6 Echocardiogram of a patient with pulmonary atresia and a diminutive right ventricle showing the echo from the small tricuspid valve RVC right ventricular cavity RVW right ventricular wall TV tricuspid valve

merely be the result of inability to locate it On the other hand simulation of valve motion is most unusual

Summary

A case of tricuspid atresia with unusual echocardiographic findings is presented The echocardiogram was successful in defining great artery interrelationships ventricular looping and cavity sizes An echo pattern resembling the motion of a small tricuspid valve was observed this was proven to be spurious at catheterization and necropsy Caution should be exercised in diagnosing the presence of a tricuspid valve on the basis of atypical echoes from the tricuspid valve area

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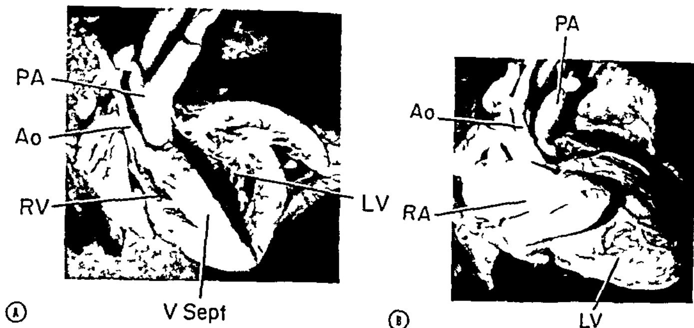


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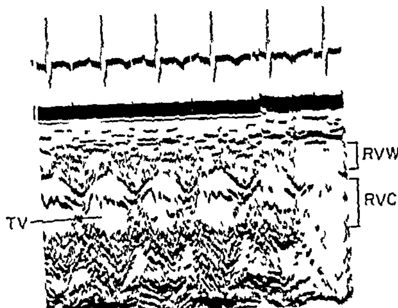


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Clinical pathologic conference

Massive myocardial necrosis in a young woman

Rimgaudas Nemickas, M D
David Fishman, M D
Thomas Killip M D
Willard Dalton M D
Gissur Brynjolfsson, M D
John Robinson, M D
Rolf M Gunnar, M D
Maywood and Evanston Ill

Case presentation

DR DAVID FISHMAN The patient was a 33 year old housewife transferred to Loyola University Medical Center on December 17, 1975 with chest pain shortness of breath, and increasing fatigability

She had been well until three weeks earlier when she noted the sudden onset of sharp retrosternal chest pain while at rest The pain was not pleuritic and lasted ten minutes Four days later the pain recurred radiated to the back, and was associated with severe dyspnea Later that day she was admitted to another hospital where digoxin furosemide and coumadin were given and her symptoms improved There was no history of fever chills hemoptysis, pedal edema or paroxysmal nocturnal dyspnea There had been no recent exposures to toxins or animals There was no history of rheumatic fever or hypertension She used oral contraceptives for an unknown period of time prior to 1972 She had noticed mild upper respiratory infection during the month prior to the onset of her illness She had been hospitalized for a dilation and curettement and an anxiety reaction during the past year She bore two children the younger of whom was 10 years old She had been taking dessicated thyroid for menometrorrhagia for 15 years She smoked less than one pack of cigarettes per day and drank two beers daily Her parents, siblings and offspring were all alive One sister had been evaluated for an arrhythmia

On examination she was a white female comfortable at rest The blood pressure was 88/68 the pulse 100/minute, the respiratory rate 20/minute Temperature was 37° C Funduscopic examination was normal The thyroid was not enlarged The jugular venous pressure was estimated above 20 cm with prominent CV waves The chest was clear A diffuse cardiac apex was felt in the fifth left intercostal space at the anterior axillary line There was a prominent left parasternal lift The first sound (S_1) was decreased The second sound (S) was closely split Ventricular (S_3) and atrial (S) gallop sounds were heard at the apex and left lower sternal border A musical grade 3/6 holosystolic murmur with no respiratory variation was heard at the left lower sternal border and a grade 3/6 holosystolic murmur of different quality was present at the apex with radiation to the left axilla A pericardial friction rub was noted along the left sternal border The abdomen was flat The liver was enlarged had a 23 cm span and was pulsatile The spleen could not be palpated The extremities revealed no clubbing or edema The rest of the examination was unremarkable

Initial laboratory data showed WBC 11 300 with 52 neutrophils 32 lymphocytes 11 mono

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Fig 1 Chest roentgenogram posteroanterior (a) and lateral (b) views

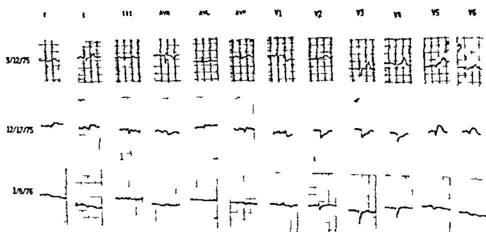


Fig 2 Electrocardiograms.

cytes 2 eosinophils and 3 basophils hemoglobin 13 8 Gm per cent and hematocrit 42 per cent Urinalysis was normal Serum sodium was 148 mEq /L potassium 4 3 mEq /L chloride 98 mEq /L CO_2 content 28 mM /L and the venous pH was 7 43 The BUN was 26 mg per cent uric acid 10 6 mg per cent calcium 8 9 mg per cent phosphates 4 2 mg per cent glucose 140 mg per cent cholesterol 120 mg per cent total protein 7 2 Gm per cent albumin 3 9 Gm per cent and total bilirubin 0 7 mg per cent The alkaline phosphatase was 70 units LDH 340 units SGOT 65 units CPK 51 units (all MM isoenzyme) The prothrombin time was 28 3 seconds and partial thromboplastin time was 48 seconds Initial ASO titer was 500 Todd units with 500 and 333 units on subsequent examinations Two throat cultures grew out normal flora Three blood cultures revealed no growth Stool examination for ova and parasites was negative T_3 resin uptake was 29 per cent T_4 M P was 7 0 $\mu g/100\ ml$ and TSH was 2 7 $\mu u/ml$.

Dr Rogelio Moncada The chest roentgenogram on admission (Fig 1) showed marked

enlargement of the cardiac silhouette involving all four chambers The pulmonary vasculature reflects increased pulmonary venous pressure basilar vasoconstriction and shifting of the pulmonary blood flow towards the upper lung fields Interstitial edema was present in the lung bases On subsequent films we failed to identify any signs of pericardial effusion

DR JOHN F MORAN A summary of selected tracings (Fig 2) from the normal tracing, prior to the onset of illness, through the last tracing showed the changes of an extensive anterolateral apical myocardial infarction, left axis deviation, complete right bundle branch block, and the progressive loss of QRS amplitude

DR PATRICK J SCANLON The echocardiogram showed a normal looking aorta and aortic valve and the left atrium was not grossly enlarged Septal contraction was fairly normal, but the posterior wall contraction was increased The diameter of the left ventricle was within normal limits Mitral valve motion was good

DR DAVID FISHMAN The patient was continued on digoxin furosemide, and coumadin Prednisone 60 mg daily and erythromycin 250 mg four times daily were added On the seventh hospital day a Swan Ganz catheter was inserted The mean right atrial pressure was 25 mm Hg, pulmonary artery pressure was 38/20 mm Hg and the mean pulmonary capillary wedge pressure was 28 mm Hg On the eighth hospital day frequent premature ventricular contractions were treated with lidocaine Nitroprusside infusion and fluid challenge did not affect the cardiac output on the ninth hospital day On the twelfth hospital day the patient deteriorated and left cardiac catheterization with angiography was performed On the thirteenth hospital day, Keflin was begun for a urinary tract infection Additional laboratory data showed no change in acute and convalescent titers to the following organisms Toxoplasma Psittacosis, Adenovirus Influenza A & B Parainfluenza 1, 2 and 3, Eaton agent Varicella Zoster, and Cytomegallic virus Fungal complement fixation studies were negative The patient s condition worsened and an intra aortic balloon pump was inserted On the twentieth hospital day, cardiac catheterization was repeated to visualize the left ventricle in a different position and to obtain coronary arteriograms On the twenty first hospital day, the patient became acidotic and thrombocytopenic She died on the twenty third hospital day

Clinical discussion

DR THOMAS KILLIP When asked to give a cardiovascular CPC one often suspects that the patient has one of three things a myxoma IHSS, or a floppy mitral valve I can confidently say that the patient had none of these This is a most puzzling case, and I am not sure how much more I will be able to deduce

Does the pain have any direct relation to the patient s heart problem? She had pain associated with severe dyspnea There may be several reasons for this One is if the pain is pleuritic and patient is unable to take a deep breath We are told the pain was not pleuritic so that is not a factor In massive pulmonary embolism there may be a sensation of dyspnea presumably secondary to sudden and acute changes in lung compliance Many patients with ischemic pain have dyspnea with the pain due to altered ventricular compliance and consequent increased left ventricular filling pressure Presumably the dyspnea in this patient reflected acute heart failure which was treated when she was admitted to the other hospital 10 days before she was transferred here

From physical examination we recognize that this young woman was severely ill She was hypotensive There were prominent CV waves in the jugular venous pulse which probably reflected significant tricuspid regurgitation We are told that she had a parasternal lift There are several causes for a parasternal lift Systolic expansion of the left atrium from mitral regurgitation displaces the anterior structures forward An overloaded dilated right ventricle is another cause as is aortic root movement in severe aortic regurgitation A fourth cause that should not be overlooked is the possibility of a left ventricular aneurysm or a dyskinetic area expanding paradoxically during systole We have enough information to suggest that she had mitral regurgitation and tricuspid regurgitation One might wonder about the possibility of a ventricular septal defect congenital or acquired but I do not think the physical findings suggest this She has an enormous liver and I presume this reflects congestion and tricuspid regurgitation The laboratory values are not of any help at this point I

am a little surprised that her liver function is not more abnormal She has valvular dysfunction and severe myocardial dysfunction We are not yet sure whether the valvular dysfunction is primary or secondary

I agree with the interpretation of the electro cardiograms. It is significant that several months before she died she had a perfectly normal elec trocardiogram Then she developed striking abnormalities which can only be interpreted as an extensive loss of anterior forces and probably some strictly posterior ischemia I am puzzled by the echocardiograms I would have predicted we would see greater evidence of increased chamber size and reduction in contractility The right heart pressures are significantly abnormal Right atrial pressure is extraordinarily high 25 mm Hg about the same as the left atrial pressure With such pressures one immediately thinks about the possibility of a constrictive or restrictive phenom ena In the presence of normal chamber size assuming the echo is correct one must consider an infiltrative process involving the myocardium Constrictive pericarditis characteristically dem onstrates essentially equal filling pressures in both ventricles a normal ejection fraction usually normal contractility and normal cham ber sizes Infiltrative processes simulate those hemodynamic findings Further interpretation of the pressures will depend on what the left ventric ular angiogram shows the size of the chambers and whether there are regional differences in contractility

At this point we ask whether her illness is acquired or a congenital defect only recently manifested? A congenital problem seems unlike ly The possibility of an A V fistula or anomalous coronary artery should be considered but the patient had been through two normal pregnancies and had obviously seen physicians previously When the left coronary artery arises from the pulmonary artery in reality an A V fistula there is premature myocardial infarction and mitral regurgitation due to papillary muscle dysfunc tion However I believe the patient is too old for this diagnosis If she truly has had a myocardial infarction as suggested by her electrocardio grams an anomaly of the distribution of the coronary artery is a possibility A massive infarc tion in a young person in whom there was a single left coronary and only a trivial right coronary artery has been reported Could this be an infec tious process? A myocarditis with extensive damage? The Coxsackie virus is one of the more common causes of adult myocarditis but titers are not available to us

How could a myocardial infarction have occurred? Was there a myocarditis or cardiomyo pathy predisposing to the formation of a clot and a coronary embolus? Unrecognized bacterial endocarditis with coronary embolus seems unlike ly We have no history of drug ingestion but with the psychiatric history one wonders about the possibility of the phenothiazine toxicity These drugs have been associated with striking electro cardiographic abnormalities and even with fatal myocardial infarction Could she have a cardio myopathy with a secondary myocardial infarc tion? This would be an unusual event The most common form of cardiomyopathy recognized or unrecognized is alcoholic One infectious disease namely Chagas is associated with electrocardio graphic abnormalities and complete RBBB but this lady is not from South America

Could this be an infiltrative cardiomyopathy such as amyloid simulating a myocardial infarc tion? There is a peculiar condition termed Fied ler s myocarditis which should be considered Fiedler s is an acute inflammatory process asso ciated with myocardial degeneration and dys function usually with eosinophilia Friedberg has described a case in which the electrocardiogram simulated acute myocardial infarction but could not be demonstrated at autopsy

From the evidence at hand we must conclude that this woman has lost a massive amount of anterior left ventricle and probably also the septum as it supports the tricuspid valve leading to a cardiomyopathy with or without aneurysm formation The etiology is not clear We may change our minds when we review the cardiac catheterization studies

Dr David Fishman The left ventricular end diastolic pressure was 25 mm Hg The left ventriculogram showed an enlarged chamber with only the base and part of the inferior wall contracting Moderate mitral regurgitation was present Coronary arteries showed no gross obstructions

Dr Thomas Killip We now have a great deal of information The question is what we can do with it I cannot escape the supposition that this

patient has had a massive myocardial infarction There are striking differences in contractility within the ventricle There is a small ring of reasonably functioning myocardium at the base But, why did this occur Birth control pills are a possible cause of coronary thrombosis but she had been off them for several years We do know, on an experimental basis, that myocardial infarction can be produced by injecting various substances which increase the platelet coagulability such as ADP, and that the platelet plugs can be found in the vessels from 10 minutes to a half hour after injection and that by two to three hours there is a diffuse myocardial infarction with no evidence of vascular obstruction Coronary spasm has also been recognized and a few patients with myocardial infarction have had perfectly normal coronary arteries on angiography Could this be a periarteritis or some sort of an inflammatory process? There is no evidence to suggest this Unfortunately, I am unable to advance a specific etiology I wonder about coronary spasm or some form of coagulation defect perhaps affecting the platelets which was evanescent but diffuse Clearly the damage involved the vast majority of the left ventricle and left the patient with a form of cardiomyopathy I cannot find evidence for a myocarditis or infiltrative disease I believe the problem is myocardial infarction with extensive loss of left ventricular mass of uncertain cause

Autopsy findings

DR GISSUR BRYNJOLFSSON The heart was quite large due to dilation of the left ventricle but weighed only 300 Gm The epicardium was smooth and glistening and there were no adhesions between the pericardial sac and the epicardium The coronary arteries were essentially normal (Fig 3) The myocardium of the anterior and lateral wall of the left ventricle was extensively replaced by fibrous tissue and the wall markedly thinned in areas measuring only 2 to 3 mm in thickness (Fig 4) This myocardial lesion involved the apex and extended within 2 5 to 3 cm of the base of the left ventricle Circumferentially, it measured up to 8 cm and extended from the septum to the posterior papillary muscle The anterior papillary muscle appeared to be completely fibrotic There was some focal fibrosis of the septum, at the base but otherwise the septum was of about normal thickness A large portion of the posterior wall of the right ventricle was paper thin, measuring only about 1 mm in thickness

The endocardium of the fibrotic portion of the left ventricle was thickened, white and opaque There was a mural thrombus at the apex of the left ventricle measuring 1 5 cm in diameter A small mural thrombus was also noted at the base of the right auricular appendage and two very small mural thrombi were noted in the superior vena cava The valves were normal There was moderate dilation of the mitral and tricuspid valve rings with the mitral measuring 11 5 cm and the tricuspid measuring 14 cm in circumference

On microscopic examination there was marked lymphocytic infiltration of the myocardium, in part focal and in part diffuse (Fig 5) with extensive loss of myocardial cells in areas (myocytolysis) and some secondary fibrosis In a large portion of the anterolateral wall of the left ventricle there was no remaining myocardium and the wall was made up of a thin layer of fibrous tissue and thickened endocardium (Fig 6) The same was true for a large portion of the posterior wall of the right ventricle where the wall in areas measured only about 1 mm in total thickness In addition, there were scattered smaller areas where the myocardium had disap

Fig 3 The epicardium is smooth and glistening with no evidence of inflammatory reaction The coronary arteries are normal

Fig 4 Cross-section of left and right ventricles There is extensive replacement of the myocardium of the left ventricle by fibrous tissue The wall is markedly thinned measuring in areas only 2 to 3 mm in thickness

Fig 5 A and B Lymphocytic infiltration of the myocardium (*A* original magnification about ×50 *B* original magnification about ×500)

Fig 6 Cross section of the left ventricle The myocardium has been entirely replaced by a thin layer of fibrous tissue The inflammatory reaction has subsided The endocardium is markedly thickened (Original magnification about ×50)

Fig 7 Heavy lymphocytic infiltration at the junction of remaining myocardium and fibrous tissue (Original magnification about ×50)


3


4


5A


5B


6


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For legends see facing page

patient has had a massive myocardial infarction There are striking differences in contractility within the ventricle There is a small ring of reasonably functioning myocardium at the base But, why did this occur Birth control pills are a possible cause of coronary thrombosis, but she had been off them for several years We do know, on an experimental basis that myocardial infarction can be produced by injecting various substances which increase the platelet coagulability such as ADP, and that the platelet plugs can be found in the vessels from 10 minutes to a half hour after injection, and that by two to three hours there is a diffuse myocardial infarction with no evidence of vascular obstruction Coronary spasm has also been recognized and a few patients with myocardial infarction have had perfectly normal coronary arteries on angiography Could this be a periarteritis or some sort of an inflammatory process? There is no evidence to suggest this Unfortunately, I am unable to advance a specific etiology I wonder about coronary spasm or some form of coagulation defect perhaps affecting the platelets which was evanescent but diffuse Clearly the damage involved the vast majority of the left ventricle and left the patient with a form of cardiomyopathy I cannot find evidence for a myocarditis or infiltrative disease I believe the problem is myocardial infarction with extensive loss of left ventricular mass of uncertain cause

Autopsy findings

DR GISSUR BRYNJOLFSSON The heart was quite large due to dilation of the left ventricle but weighed only 300 Gm The epicardium was smooth and glistening and there were no adhesions between the pericardial sac and the epicardium The coronary arteries were essentially normal (Fig 3) The myocardium of the anterior and lateral wall of the left ventricle was extensively replaced by fibrous tissue and the wall markedly thinned, in areas measuring only 2 to 3 mm in thickness (Fig 4) This myocardial lesion involved the apex and extended within 2 5 to 3 cm of the base of the left ventricle Circumferentially, it measured up to 8 cm and extended from the septum to the posterior papillary muscle The anterior papillary muscle appeared to be completely fibrotic There was some focal fibrosis of the septum at the base, but otherwise the septum was of about normal thickness A large portion of the posterior wall of the right ventricle was paper thin, measuring only about 1 mm in thickness

The endocardium of the fibrotic portion of the left ventricle was thickened, white and opaque There was a mural thrombus at the apex of the left ventricle measuring 1 5 cm in diameter A small mural thrombus was also noted at the base of the right auricular appendage and two very small mural thrombi were noted in the superior vena cava The valves were normal There was moderate dilation of the mitral and tricuspid valve rings with the mitral measuring 11 5 cm and the tricuspid measuring 14 cm in circumference

On microscopic examination there was marked lymphocytic infiltration of the myocardium, in part focal and in part diffuse (Fig 5) with extensive loss of myocardial cells in areas (myocytolysis) and some secondary fibrosis In a large portion of the anterolateral wall of the left ventricle there was no remaining myocardium and the wall was made up of a thin layer of fibrous tissue and thickened endocardium (Fig 6) The same was true for a large portion of the posterior wall of the right ventricle where the wall in areas measured only about 1 mm *in total* thickness In addition there were scattered smaller areas where the myocardium had disap

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Fig 3 The epicardium is smooth and glistening with no evidence of inflammatory reaction The coronary arteries are normal

Fig 4 Cross section of left and right ventricles There is extensive replacement of the myocardium of the left ventricle by fibrous tissue The wall is markedly thinned measuring in areas only 2 to 3 mm in thickness

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Fig 6 Cross section of the left ventricle The myocardium has been entirely replaced by a thin layer of fibrous tissue The inflammatory reaction has subsided The endocardium is markedly thickened (Original magnification about ×50)

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peared The inflammatory reaction and myocytolysis involved all chambers of the heart and extends into the superior vena cava The cell infiltrate was often heavy at the advancing edge of the lesions i e at the junction between the areas of myocytolysis and the remaining myocardium (Fig 7) In the older fibrotic areas most of the lymphocytes had disappeared In one of the sections from the right ventricle two multinucleated giant cells were seen There were a few small foci of recent hemorrhage and focal hemosiderin deposits There were no primary vascular changes

The endocardium especially of the left ventricle was markedly thickened due to proliferation of modified smooth muscle cells separated by mucoid material which on colloidal iron staining gave a deep blue color There was also moderate increase in elastic tissue in the endocardium The mural thrombus of the apex of the left ventricle showed considerable organization The mural thrombi of the right atrium and superior vena cava showed early organization Sections of the SA node revealed focal lymphocytic infiltration with loss of some nodal cells and secondary fibrosis Other findings included chronic passive congestion of the lungs and the liver moderate generalized edema moderate hydrothorax bilateral and ascites bronchopneumonia and marked fibrosis and atrophy of the thyroid with the gland weighing only 4 2 Gm

The histologic findings in this case indicate that the myocardium was being destroyed by the lymphocytes (killer cells) It is considered likely that this patient had a viral myocarditis although no virus was found on electron microscopy and then developed a delayed hypersensitivity reaction with myocytolysis brought about by the lymphocytes The reactive fibrosis appears to be a great deal less than in healing infarction

DR THOMAS KILLIP Did you look at the skeletal muscle?

DR GISSUR BRYNJOLFSSON Yes it was normal

DR THOMAS KILLIP Do you have any speculation as to why the free wall of the left ventricle was primarily involved extending into the septum? One would have thought that an inflammatory process would diffusely involve the entire myocardium

DR GISSUR BRYNJOLFSSON Yes it did involve the entire myocardium but was not grossly visible throughout Every section from the left ventricle and the septum where it looked grossly normal showed lymphocytic infiltration The same was true of the right ventricle and both atria

DR ROBERT CROKE Do you suppose there is any connection between the thyroid and the myocardium?

DR GISSUR BRYNJOLFSSON I do not think so I think that the thyroid lesion was there for a long time We quite often see thyroids like this

Comments

DR JOHN ROBINSON I think this is a rather impressive example of the extreme lymphocyte cytotoxicity It is beneficial when directed towards a tumor It is unfortunate when it is directed towards the myocardium These infiltrating lymphocytes indicate they are there for an immunologic reason There must be new or changed antigens in the myocardium Since there is no reason to think she had primary antigenic alteration of muscle structure it is probably viral induced Multiple auto antibodies including myocardial were looked for but none were found

In response to Dr Killip s query about skeletal muscle pathology patients with polymyositis have involvement of skeletal muscle but not ventricular muscle The lymphocytes from these patients when incubated in vitro with normal myoblasts can destroy muscle cells within 4 hours You actually do not even need the lymphocytes there You can just simply take the supernatants from stimulated lymphocytes and rapidly kill muscle cells in vitro So I think we can envision the pathogenesis of this patient s rapid cell loss and electrical changes occurring in ventricular muscle but we certainly do not have any specific etiology

DR THOMAS KILLIP Dr Gunnar what was your clinical diagnosis when the patient died?

DR ROLF M GUNNAR We thought she had a viral myocarditis

DR THOMAS KILLIP Did you feel the electrocardiograms were compatible with that?

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ence with endomyocardial biopsy, and the technique seems simple and safe I wonder if in this patient a transvenous myocardial biopsy might have given indication of something more than just myocarditis in view of the massive accumulation of lymphocytes

DR GISSUR BRYNJOLFSSON It is very possible we would have seen lymphocytic infiltration, it was that diffuse

DR ROLF M GUNNAR I think it is a very important point in some of these desperately ill people Because if we had seen her early and made the correct diagnosis, one wonders what effect large doses of steroids or other immunologically active agents would have had on this process

DR JOHN ROBINSON Actually, we did consider immunosuppressive therapy in this patient But in this patient with marked fibrosis, it would have been fruitless The important point here is that if you could detect lymphocytic infiltration earlier, you definitely would be justified in trying to turn off that response Immediate treatment possibly with steroids, but for long term effects I think you would have to consider azathioprine or cyclophosphamide to prevent lymphocyte cytotoxic responses Antilymphocytic serum may be of value

DR THOMAS KILLIP Well I want to congratulate Dr Brynjolfsson I have never seen a case like this It was extraordinary and obviously he put a great deal of work into the study of the case One desperately wants to know the *why* of this process We have a little bit of the *how* If you find any more cases let us know I hope you do not see any more, because I think this is the most frightening process I have been presented with in a long time

Contemporary medical management of stable angina pectoris

H. Dirk Sostman M D
Rene A Langou M D
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This review will discuss approaches currently available in the United States for the treatment of "stable" angina pectoris due to atherosclerotic coronary artery disease These include modification of life style treatment of associated diseases various nitrate compounds the beta adrenergic blocking agent propranolol and physical conditioning programs

In the interest of clarity more poorly understood forms of angina such as angina with angiographically normal coronary arteries [1] and a variant or Prinzmetal s angina will not be discussed. Space limitations preclude consideration of unusual and as yet unproven—therapeutic agents such as perhexiline verapamil [4] and diphenylhydantoin [5] or of beta receptor blocking drugs not available in the United States The latter subject is reviewed in detail by Prichard

Understanding the physiology of and circulatory responses to anginal pain is essential to the rational management of coronary artery disease Hence these topics will be discussed briefly Additionally some of the problems inherent in assessment of response to treatment will be mentioned since they are important both to practical clinical management of individuals with angina and to evaluation of therapeutic modalities

Physiology of angina pectoris

It is generally accepted that the primary pathophysiologic process causing anginal pain is the inability of diseased coronary arteries to provide adequate blood flow to meet the oxygen requirements of the myocardium at a particular time The determinants of this imbalance between supply and demand are complex

While coronary artery stenosis is the sine qua non of typical angina it is not sufficient to explain the development of anginal pain other factors which may contribute to reduced oxygen delivery to the myocardium include coronary—artery spasm or vasoconstriction and abnormal blood oxygen transport [21] The medical approach to increasing oxygen delivery to the myocardium has been based upon the use of vasodilator drugs which while successful in increasing myocardial blood flow in normal hearts have been uniformly ineffective in diseased coronary circulations [22,23] At the present time attempts to increase total oxygen transport to the myocardium are within the province of surgical therapy

Reduction of myocardial oxygen demand is the cornerstone of current medical therapy of angina The total oxygen consumption of the heart depends upon several factors of differing importance [24-27] Of lesser quantitative importance are the basal metabolism of the myocardium external contractile element work and the activation energy required for depolarization and electromechanical coupling The major determinants of myocardial oxygen consumption (MVO_2) are the systolic wall tension the relative amount of time during which systolic wall tension is exerted and the inotropic state of the heart The ventricular systolic wall tension (T) is a function of ventricular dimensions (directly proportional to radius (r) and inversely proportional to thickness (h)) and developed pressure (P) so that

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$T = Pr/2h$, the Laplace relationship for a spheroid chamber From this expression the oxygen costs of cardiac dilatation and systemic (and therefore intraventricular) hypertension may be appreciated The time during which systolic wall tension is exerted is governed by the heart rate (the frequency with which tension must be developed) and probably[4,7] the ejection time (the fraction of each cardiac cycle during which tension must be maintained) The heart rate, of course, also influences myocardial perfusion by changing the duration of diastole, contractility,[28] and probably the distribution of coronary blood flow[5,29,30] The product of tension and heart rate expresses the internal contractile element work of the heart This and the contractility of the ventricle are the chief determinants of MVO_2 The effect of inotropic stimuli on MVO was appreciated from studies of the effects of sympathetic nerve stimulation[31] and catecholamine administration,[3] and has been shown in an isolated left ventricle preparation to have about the same influence on MVO_2 as systolic wall tension[33] This explains the clinical observation that digitalis preparations may reduce the frequency or severity of anginal attacks when administered to patients with heart failure and ventricular dilatation the decrease in developed tension more than offsets the increase in MVO_2 due to the inotropic effect of the glycoside[34]

The precipitation of an anginal attack must involve the factors outlined above The sequence of changes may be variable depending upon the patient's baseline state psychologic factors[35] and the stress exerted upon him but certain relatively constant hemodynamic changes have been described in the experimental settings of exercise and atrial pacing[5,36,3] Myocardial ischemia results in a state of abnormal ventricular function characterized by increased left ventricular end diastolic pressure (LVEDP) This has been interpreted as acute reversible heart failure[38] or as decreased diastolic compliance[39] Abnormal elevations of LVEDP are associated with shifts of the ventricular function curve downward and to the right, stroke volume and work are subnormal[40] Consequently ventricular wall tension increases further increasing MVO[41] and reducing subendocardial blood flow[4] Peripheral vasoconstriction manifested by increased systemic arterial pressure occurs[43] increasing afterload and thus ventricular wall tension Regional wall motion abnormalities might conceivably result in increases in contractility in unaffected regions of the myocardium[40] These changes precede and accompany the development of pain The pain itself and reflex sympathetic outpouring may accentuate contractility and afterload further increasing MVO Reflex coronary artery vasoconstriction on a neurogenic basis[19] might result in decreased oxygen supply to the heart as a result of anginal pain The hemodynamic changes are reversed by termination of exercise and the accompanying decrease in venous return adrenergic output and their concomitants That the hemodynamic changes can be prevented or reversed, forms the basis of medical therapy

Basis for medical therapy of angina

The roles of smoking diet, and style of life in the prevention of coronary artery disease are *controversial in varying degrees*[44,47] but *most* physicians agree that they are important areas for intervention in managing patients with angina

Smoking cigarettes can be an important precipitating factor in angina pectoris There are two main reasons for this Systemically absorbed nicotine increases heart rate and both systolic and diastolic arterial pressure[48,49] Absorbed carbon monoxide decreases blood oxygen content and depresses left ventricular function It is evident that these changes decrease the patient's hemodynamic reserve and make him liable to angina from lesser stresses and at lower levels of cardiac work In some patients smoking a cigarette may itself be sufficient to precipitate an anginal attack Although this view is not universally accepted[45] we have found that cessation of smoking is symptomatically *beneficial to most* anginal patients Achieving patient compliance is *obviously not easy The physician must take a* serious approach and spend sufficient time *discussing smoking* with the patient a good physician-patient relationship is more essential in this (and in other attempts to modify habitual behavior) than in any other aspect of the treatment of anginal patients Judicious use of minor tranquilizers may be of slight benefit

We place less importance on management of the patient's diet than on cessation of smoking Weight reduction would appear to be psychologically helpful and to reduce systemic and thus cardiac work but this is not definitively established[50] *Diet or (if necessary) drug induced* lowering of blood lipids is probably helpful[48,51] in *our experience* patients generally accept such a

prescription well The current large selection of palatable foods containing polyunsaturated fats (and the national advertising campaigns mounted by some food manufacturers) are helpful to the physician s efforts In case the physician feels cast in the role of denier of life s pleasures it should be noted that there is no demonstrable relation between coronary artery disease and ethanol consumption[52]

The subject of life style is somewhat more diffuse Specifically, heavy meals and exertion in very hot cold or windy weather should be proscribed[3] Beyond this Aronow s statement that the patient should be guided away from stress [5] is succinct and about as specific as is usefully possible If at all possible we do not recommend that a patient cease pleasurable activities because they are associated with angina one of the important rationales for drug therapy is to help preserve the quality of life It may be helpful for the patient to work shorter more regular hours take more frequent vacations and have regular exercise and recreation The physician should if possible take an active role in helping the patient with emotional problems resulting from or contributing to his angina Given the usual time constraints of medical practice this often has less than satisfactory results We have found minor tranquilizers beneficial in some cases formal psychotherapy may some times be indicated A helpful—indeed essential—but sometimes neglected measure is discussion with the patient s family of his need for reassurance and a less stressful life style

It is essential that associated conditions which predispose the patient to angina should be vigorously treated Chronic pulmonary disease which hampers blood oxygenation should be treated in the most aggressive manner possible of course theophylline compounds and beta adrenergic agonists are clinically often found to exacerbate angina Conversely beta adrenergic—blockers which are not cardioselective usually are of limited use in the anginal patient with obstructive pulmonary disease in which there is a significant bronchospastic component Control of systemic arterial hyperten ion may be of significant benefit presumably by reducing the systolic wall tension which the ventricle must develop Treatment of congestive heart failure and particularly cardiac dilatation with digitalis and diuretics may decrease MVO and reduce the potential for angina Digitalis may have an additional role in medical treatment of angina in combination with the cardiodepressant beta blocking drugs in patients with abnormal ventricular function[55, 56] Exercise limitation due to failure can often be avoided[55] presumably by retaining the negative chronotropic action of the beta blocker while countering its negative inotropic effect[56] Digitalis may also be useful in patients with nocturnal angina one cause of which is probably acute congestive failure due to fluid shifts into the pulmonary circulation and mobilization of edema fluid[31] Anemia and hemoglobin abnormalities can impair oxygen delivery and should be reversed if possible Drugs taken for other medical illnesses which directly or indirectly affect the heart such as thyroid and steroid hormones sympathomimetic and anorexic agents should be reviewed and if possible discontinued Premature ventricular beats as well as both brady and tachyarrhythmias have been associated with increases in angina and appropriate treatment with drugs or an artificial pacemaker may significantly alleviate angina[5] Hyperthyroidism which increases systemic and myocardial oxygen demands and hypothyroidism which may accelerate atherogenesis should be identified and treated Initiation of thyroid replacement should be done carefully consultation with an endocrinologist is often helpful

Reduction of myocardial oxygen demands at a particular level of activity and thus promotion of greater activity or less frequent pains can be achieved theoretically in several ways Reduction of heart rate decrease in inotropic state of the ventricle and reduction in ventricular filling pressures are the major points of attack Other factors which may alleviate angina at least partially through the above mechanisms are promotion of a psychologic sense of health decreasing the circulatory demands of exercise reduction in adrenergic drive promotion of collateral vessel formation and redistribution of regional myocardial blood flow

Nitrates

The first line pharmacologic agent in the treatment of angina is nitroglycerin During the past several years other nitrate esters have found extensive use in management of patients with coronary artery disease and oral and cutaneous administration have become popular There is still some uncertainty concerning the modes of action of nitrates and the efficacy of long

acting compounds in various formulations and routes of administration is a matter of considerable controversy

The basic action of nitrates is vascular smooth muscle relaxation [37] As they are currently used, the effects on other smooth muscle is not clinically significant

The mechanisms by which nitrates relax vascular smooth muscle is poorly understood but they may act through cyclic AMP [37] There is a differential effect, with greater relaxation of venous smooth muscle, dilation of postcapillary resistance vessels and capacitance vessels, and significant venous pooling of blood [59, 61] There is a modest precapillary resistance vessel dilation,[17, 60, 6] although one study[60] found no change in total systemic vascular resistance Systemic arterial systolic and mean pressures are lowered through arteriolar dilation and reduction in preload (and thus stroke volume) [60, 63] Lowered arterial pressure causes a reflex increase in heart rate and contractility [63, 65] There is also a direct effect on contractility [3] The peripheral venous pooling results in decreases in LVEDP[60, 65, 66] and left ventricular end diastolic volume[60, 62, 67] and in pulmonary artery pressure [65] Left ventricular ejection rate [60, 67] and dp/dt[65] are increased

The rationale for the use of nitrates in angina is clear from the hemodynamic changes listed above The decreases in venous return, ventricular filling pressure, and ventricular dimensions reduce wall tension, as does afterload reduction Increased ejection rate and decreased ejection time due to afterload reduction and augmented inotropic state probably also reduce MVO_2 The tendency toward increased MVO_2 due to increases in heart rate and contractility is apparently offset by the beneficial hemodynamic changes induced by the drug

The nitrate induced hemodynamic alterations are probably sufficient to explain the clinical results obtained with nitrates, effects on the coronary circulation itself are disputed It is known that an index of MVO_2 the triple product of heart rate, systolic pressure and ejection time at onset of angina is unchanged by nitrates [27, 64, 67] This suggests that nitrates lower MVO_2 at a given level of body work and do not increase oxygen delivery to the myocardium Although it has been stated that nitrates cause coronary vasodilation,[68, 69] intracoronary arterial administration of nitroglycerin fails to alleviate angina induced by pacing [70] while sublingual nitroglycerin reduces MVO_2 and relieves angina[71] by its peripheral circulatory effects Studies of total,[72, 74] regional,[75, 77] and subendocardial[77, 78] coronary blood flow have yielded contradictory results, although definite conclusions do not seem justified yet some authors state that, while leaving total myocardial blood flow unchanged nitroglycerin increases subendocardial blood flow in both normal and ischemic regions of the ventricle [77] There is little work on the effects of other nitrates on the coronary circulation

The prompt onset of action of sublingual nitroglycerin makes it uniquely suitable for therapy of acute ischemic pain,[79] but its transient effect renders it ineffective in the prophylaxis of angina Four avenues to prolonged nitrate action have been pursued thus far organic nitrate esters alleged to be intrinsically long acting used sublingually or orally, sustained-release oral nitroglycerin preparations, and topical nitroglycerin

Studies of "long acting nitrates have demonstrated effects persisting longer than the usual effect of sublingual nitroglycerin [80, 86] In many of these reports, use of non equipotent doses makes interpretation difficult [78, 87] and the substitution of hemodynamic effects for antianginal effects may lead to erroneous conclusions [88] Other studies have failed to show any advantage of long acting nitrates[67] or have even shown them to be no more effective than placebo [89, 90] Nevertheless these drugs are widely used clinically, and are thought effective, since the usual dose in clinical use is greater than the equipotent dose of nitroglycerin,[67] a longer duration of action with some suitability for prophylactic use is not surprising Chewable[91] or oral[86] formulations can give longer lasting hemodynamic effects, their antianginal effects have not yet been evaluated conclusively although a recent ergometric study[92] suggests considerable benefit two hours after administration of oral isosorbide dinitrate

The development of sustained-release preparations of the inherently short acting nitroglycerin has been surrounded by similar controversy [81] Although there is ample data documenting their sustained physiologic effects,[86, 93, 95] and some data concerning effect on exercise tolerance [96] there is still no comprehensive evaluation of their use in treatment of angina This is surprising since oral nitroglycerin offers great potential advantages

Topical application of nitroglycerin as an ointment has been known for a long time [97] but only

recently has there been much interest in its use Hemodynamic effects persisting for three to six hours have been reported,[98 101] and two studies[90 102] convincingly demonstrated improved exercise tolerance from one to three hours after administration Nitroglycerin ointment is one of the nitrate formulations proven to have long lasting effects on angina It has found extensive recent clinical use in patients with nocturnal angina and tentative proof of its efficacy lends inferential support to the use of sustained-release nitroglycerin

Since there is no evidence for tachyphylaxis cross tolerance or post withdrawal rebound phenomena[6 7] with therapeutic doses of any currently used nitrate preparation it appears that prophylactic nitrate therapy is not harmful Nitrate induced hypotension can result in syncope and may be dangerous in patients with cerebrovascular disease but the hypotension is not greater than that caused by nitroglycerin itself although subject to the same cautions For nocturnal use nitroglycerin ointment seems preferable on the basis of available data its inconvenience often precludes its use for ambulatory patients during the daytime The prophylactic nitrate preparation to use during the daytime remains a matter of personal preference and individual result no currently available drug or formulation has yet been conclusively recognized as efficacious Frequent administration of sublingual nitroglycerin is a less convenient if perhaps more effective alternative[88] *but is is doubtful* that satisfactory compliance with this regimen can be achieved

If nitrates are used without propranolol the optimum dose can be selected by the effect on blood pressure and heart rate The greatest attainable decrease in blood pressure which is not attended by symptoms of hypotension (especially during orthostasis) intolerable headache or increase in resting heart rate of greater than 10 to 15 beats per minute indicates optimum nitrate therapy As Goldstein and Epstein[8] have pointed out headache should not be used as a therapeutic endpoint We have not found that it is often a limiting factor in therapy provided analgesics are given initially and the patient is reassured that it will diminish The other physiologic results of nitrate therapy may limit the use of nitrates however and it is in these patients or in those in whom optimal nitrate therapy fails to control angina that propranolol is most valuable

Propranolol

Propranolol is well absorbed after oral administration and peak levels in the blood occur 1 to 2 hours later[103] It is eliminated by hepatic clearance[103] with a biologic half life of 2 to 4 hours after intravenous administration[1 3] but a reduced clearance leads to a half life of 4 to 6 hours after chronic oral administration[103] The clearance may be increased in patients with renal disease[104] It is 90 to 96 per cent bound when measured in the plasma of normal subjects[105] The bioavailability of the drug given orally is low Most of the absorbed dose is cleared from portal blood in the first pass through the liver by a saturable mechanism the availability of small oral doses of the drug is very low but that of larger doses is disproportionately greater[106] The clinical implication of this is that initial small oral doses of the drug will serve mostly to saturate liver binding sites producing small systemic effects During chronic oral administration hepatic tissue binding sites probably remain saturated throughout the conventional dosage interval[1 7 108] Large inter individual variations in plasma drug levels have been observed in human subjects receiving equal doses[103] the pharmacologic *and clinical* effects of the drug appear to correlate reasonably well with plasma levels[1 9] although the degree of beta blockade *may be a more* meaningful index[109]

The hemodynamic properties of beta blockers have been extensively reviewed by Gibson[110] The heart rate is decreased in normal subjects[1] and in patients with ischemic[112] and other organic[1 9] heart disease at rest and during stress[113] and after nitroglycerin administration[14] The reduction in heart rate is related to the plasma propranolol *concentration*[111] *and* the effects of beta blockade do not significantly differ in normal subjects and in patients with ischemic heart disease[11] There is *a decrease* in cardiac output,[1 9 115 11] with no change in stroke volume[1] which parallels the lowering of heart rate[110] but is not prevented in normals or patients with heart disease by artificially holding heart rate constant[116 117] Systolic ejection rate is lowered by propranolol[11] The rate of rise of left ventricular pressure is reduced at *rest and* during exercise[5 1] The left ventricular end-diastolic pressure is usually increased[5 1 8] but may even be reduced[119] A change in ventricular compliance has been suggested as the mechanism for the latter observations in the case of practolol End diastolic

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The nitrate induced hemodynamic alterations are probably sufficient to explain the clinical results obtained with nitrates, effects on the coronary circulation itself are disputed It is known that an index of MVO_2, the triple product of heart rate systolic pressure and ejection time at onset of angina is unchanged by nitrates [27 64 67] This suggests that nitrates lower MVO_2 at a given level of body work and do not increase oxygen delivery to the myocardium Although it has been stated that nitrates cause coronary vasodilation,[68 69] intracoronary arterial administration of nitroglycerin fails to alleviate angina induced by pacing,[70] while sublingual nitroglycerin reduces MVO_2 and relieves angina[71] by its peripheral circulatory effects Studies of total,[72 74] regional,[75 77] and subendocardial[77 78] coronary blood flow have yielded contradictory results, although definite conclusions do not seem justified yet, some authors state that, while leaving total myocardial blood flow unchanged nitroglycerin increases subendocardial blood flow in both normal and ischemic regions of the ventricle [37] There is little work on the effects of other nitrates on the coronary circulation

The prompt onset of action of sublingual nitroglycerin makes it uniquely suitable for therapy of acute ischemic pain [79] but its transient effect renders it ineffective in the prophylaxis of angina Four avenues to prolonged nitrate action have been pursued thus far organic nitrate esters alleged to be intrinsically long acting used sublingually or orally, sustained-release oral nitroglycerin preparations, and topical nitroglycerin

Studies of "long acting' nitrates have demonstrated effects persisting longer than the usual effect of sublingual nitroglycerin [80 86] In many of these reports, use of non equipotent doses makes interpretation difficult,[78 87] and the substitution of hemodynamic effects for antianginal effects may lead to erroneous conclusions [88] Other studies have failed to show any advantage of long acting nitrates[87] or have even shown them to be no more effective than placebo [89 90] Nevertheless, these drugs are widely used clinically, and are thought effective, since the usual dose in clinical use is greater than the equipotent dose of nitroglycerin,[67] a longer duration of action with some suitability for prophylactic use is not surprising Chewable[91] or oral[86] formulations can give longer lasting hemodynamic effects, their antianginal effects have not yet been evaluated conclusively, although a recent ergometric study[92] suggests considerable benefit two hours after administration of oral isosorbide dinitrate

The development of sustained-release preparations of the inherently short acting nitroglycerin has been surrounded by similar controversy [81] Although there is ample data documenting their sustained physiologic effects,[86 93 95] and some data concerning effect on exercise tolerance,[96] there is still no comprehensive evaluation of their use in treatment of angina This is surprising, since oral nitroglycerin offers great potential advantages

Topical application of nitroglycerin as an ointment has been known for a long time [97] but only

congestive heart failure The myocardial depres sant *actions of propranolol* can usually be managed with standard therapy[1 4] it is wise to consider digitalis or diuretic therapy in patients with even minimal signs of heart failure [1] [4 1] Propranolol may be especially hazardous in patients with sinus node dysfunction [1] Although it has been suggested that the occurrence of asthma may not require drug discontinuation [1] asthma and obstructive lung disease are often worsened intolerably Patients on high doses of propranolol often report muscular weakness and fatigue Peripheral vascular disease may be accen tuated by beta blockade but reported cases are few Most serious reactions can be avoided by careful patient selection

Cessation of propranolol administration may pose special hazards of myocardial infarction or increased angina [2] [3] A true rebound syn drome is suggested by changes in pattern of angina *and the occurrence of infarction but the* mechanism is obscure It is possible that the phenomenon represents progression of the disease or alterations in numbers of receptor sites controlled studies have not been done It is presently considered advisable to taper the drug over a few days if cessation of therapy is neces sary[1 8]

Reported drug interactions are few Catechol amine depleting agents may potentiate the effects of propranolol[153] Propranolol may inter fere with circulatory compensation responses to anesthesia Propranolol induced bradycardia may be potentiated by digitalis intoxication

For most patients with angina propranolol represents a safe and remarkably effective mode of therapy If patients are carefully evaluated and propranolol administration is begun cautiously few adverse reactions will occur In higher risk patients the use of propranolol may still be worth *consideration* although monitoring of therapy assumes *greater* importance and adjunctive treat ment with other agents *may be necessary*

Nitrate and propranolol therapy

It has long been thought that nitrates and beta adrenergic receptor blocking agents would exert synergistic or additive effects on myocardial oxygen consumption by their opposing circula tory effects [5 56] Measurements *of exercise* capacity[65] [56] and hemodynamic parameters[65] and clinical experience support this view The addition of propranolol to nitrate therapy has

Table I Hemodynamic and other alterations usually induced by propranolol nitrates and combined therapy

Parameter	*Propranolol*	*Nitrates*	*Combined*
HR	↓	↑	↓
CO	↓	0	↓
LVSP	↓	↓	↓
SAP	0	↓	↓
SER	↓	↑	↓
LVEDP	↑	↓	↓
LVV	↑	↓	0
dp/dt	↓	↑	↓
TTI	↓	↓	↓
CVR	↑	↓	
SAP	↑	↑	

↑ = increase ↓ = decre se 0 = small or v riable effect Abbrevia tions HR = h rt rate CO = card ac output LVSP = left ventric ular systolic pressure SAP = systemic arterial pressure SER = sys tolic ejection rate LVEDP = left ventricular end-diastolic pressure LVV = left ventricular lume dp/dt = rate of rise of systolic pres sure TTI = tension time index at a given workload CVR = coronary vascular resistance SEP = subendocardial perfu n.

been suggested to improve life expectancy in an uncontrolled series [59] Currently most anginal patients in our institution are treated with combined nitrate and propranolol therapy

The rationale for combined therapy *centers on* the often opposing hemodynamic actions of the two classes of agent each should cancel the actions of the other which tend to increase MVO while the beneficial actions should usually be additive A cardiac catheterization study has proved this assumption to be *correct* both at rest and during exercise in patients with *ischemic* heart disease[65] A summary of the *hemodynamic* effects of the two classes of drug *and of their* combination is shown in Table I Significantly propranolol *prevents* nitrate induced tachycardia and increased *contractility* but does not prevent the *nitrate* induced reduction in left *ventricular* end diastolic pressure and (probably) in ventric ular volume The reduction in systemic arterial pressure and tension-time index may be additive no adverse alterations occur

The effects *of* continued therapy on the coro nary circulation must also be considered in this *instance* only hypothesis is possible for there is no experimental data It is of interest though that both propranolol and nitrates are thought *to* increase subendocardial blood flow Both agents reduce systolic wall tension but have different *effects* on diastolic perfusion Nitrates reduce diastolic wall tension by reducing ventricular size

volume usually increases[110] *Systemic arterial* pressure is lowered at doses which lower cardiac output, *at lower doses there* may be a pressor effect, which has been attributed to blockade of beta adrenergic vasodilation[110] There may be a reduction of plasma volume[111] The MVO in man is decreased at rest[113] and during exercise[114] Some of the hemodynamic changes persist after withdrawal of beta blockade[115] A potentially deleterious effect is increased coronary vascular resistance[113, 124], there is a consistent decrease in coronary blood flow,[65, 118, 114] which may be partially a result of the lessened oxygen require ments of the myocardium Although it is usually thought that local factors achieve maximum *vasodilation in ischemic myocardium, coronary* artery vasoconstriction has been proposed as a contributing factor in angina[19] and in this light, removal of the adrenergic vasodilation must be viewed with some concern A possibly beneficial effect of propranolol on the coronary circulation is increased perfusion of the subendocar dium,[116, 117] the region most vulnerable to ische mia[4] The drug also shifts the—oxyhemoglobin dissociation curve to the right[118] Propranolol also restores normal platelet aggregability in patients with angina,[119] an action which may interfere with the possible role of platelet aggregation in the pathogenesis of myocardial ischemia[119, 130]

The rationale for use of propranolol in the *treatment of angina pectoris is clear from exami* nation of its pharmacologic properties The drug decreases *MVO* by *actions upon all of its major* determinants Systemic arterial pressure, a factor in the ventricular systolic wall tension, myocar dial contractility, and heart rate are all signifi cantly affected Detrimental effects due to depression of cardiac performance, increase in ventricular volume and prolongation of ejection time do not seem to outweigh the drug s beneficial effects In a review of 331 patients studied between 1965 and 1969 78 per cent responded favorably to propranolol therapy[131] A subse quent review[10] and several recent clinical trials[56, 109, 119, 131, 136] document substantial clinical and objective exercise tolerance improvement The consideration of propranolol therapy is accompanied by two major questions the suit ability of the patient and the proper dose The *conservative* approach is to reserve propranolol for those patients who, after treatment of asso *ciated disorders* and maximal nitrate therapy still find that angina significantly interferes with *their daily life* In our opinion, the patient s subjective report is the only relevant guide in this decision In modern practice, most anginal patients are eventually treated with propranolol Since the blood levels of propranolol obtained from equal oral doses vary greatly[103, 104] the magnitude of the drug s effects depends upon the prevalent sympathetic tone[11] and since serious adverse reactions are possible,[135] initiation of therapy even by the oral route should be cautious Fortunately adverse effects usually occur early in therapy, *unfortunately, they are* not usually dose dependent and often occur with *small initial doses*[10, 137] *The usual practice in our* institution is to begin therapy with 20 mg four *times* a day and to double the dose every few days until a therapeutic end point is reached, some cardiologists prefer to initiate therapy with a shorter dosage interval for the first few doses The resting pulse rate is a convenient physiologic guide of drug effect, the usual end point is a resting pulse of 45 to 55 beats per minute It has been suggested that the peak exercise heart rate is a superior measure of therapeutic effect and that spurious medical failures may result from reliance on the resting pulse rate as a measure of adequate beta blockade[11] Other end points include nausea or diarrhea and relief of anginal symptoms About 70 to 85 per cent of patients report a significant decrease in frequency of angina[10, 56, 1, 131, 136] and ergometric testing documents improvement in exercise tolerance in this group[10, 10, 110, 11, 135] It is *impossible to predict* which patients will not respond At maximal doses exercise tolerance may not improve[139] *and clinical improvement* may seem negligible if the pretreatment anginal frequency is low[140] *The reported effective* dose ranges from 80 mg per day[135, 141] to more than 2 000 mg per day[10] *the majority of patients* require 160 mg to 320 mg per day

The adverse effects of *propranolol are largely* pharmacologic effects that arise predictably as a result of its pharmacologic actions *Life threat* ening bradycardia and shock or angina complete heart block ventricular fibrillation *and con* gestive heart failure have been report ed[13, 138, 142, 143] Serious *but not life threatening* reactions included hypotension[137, 142] lesser de grees of heart block[138] gastrointestinal[13, 1] *and* neurological[118, 14, 143] disturbances Hypoglycem ia[110, 137] and sodium retention[110, 139] *are probably* not serious except in insulin dependent diabetic patients[137] and in *individuals with severe*

this situation evaluation of propranolol therapy should include measurement of peak exercise heart rate

There are a number of published exercise programs for conditioning of anginal patients[160-163, 116] The pertinent characteristics of these have been reviewed by Wolfson and Costin[1, 5] Patients should be preselected by a general medical evaluation and a stress test should be performed in order to exclude patients in whom vigorous exercise is likely to be hazardous to establish a baseline at which work load should begin and to establish a heart rate guideline to limit peak exercise It is usual for anginal patients to take nitrates before and if necessary during exercise Exercises should not take place after a meal A warming up period should precede maximal exercise and a cooling off period should follow it Supramaximal effort is deleterious The workload is increased at regular intervals Resuscitation equipment and personnel should be available at least for high risk patients

Marked improvements in exercise tolerance can usually be found within 6 weeks after beginning an exercise program Documentation of improvement by serial exercise testing provides psychological benefit to the patient and a contemporary guideline for the physician Exercise in the coronary patient should be thought of in the same way as drug therapy both should be continued indefinitely The risks of a properly conducted physical conditioning program are small minor orthopedic complaints which do not require specific therapy are the most common complication One poorly quantifiable but unique benefit of physical training is psychological most patients report a reduced fear of their disease an improved body image and a generally more positive attitude

Evaluation of therapy

Assessment of the results of therapy of angina is important both to practical clinical management of individual patients and to comparison of therapeutic modalities in the setting of a clinical *trial* The usual methods are evaluation of patient s subjective reports of the results of therapy statistical treatment of numerical parameters such as consumption of nitroglycerin tablets or frequency of anginal attacks[1, 2, 13, 16] and the standardized exercise test[47, 1, 2, 13, 3, 60, 175]

Subjective reports from the patient concerning the efficacy of therapy are the mainstay of clinical practice This approach is often disparaged as unscientific and prone to bias or placebo effect but, as Feinstein[11, 176] has pointed out the direct consequences of angina to the individual patient concern more than ergometry For this reason simple history taking is the most effective mode of evaluation of results of therapy in daily practice In the same setting the consumption of nitroglycerin may be a useful index if account is taken of external factors which may influence it Use of subjective or semi subjective parameters in clinical trials may complement ergometric data if questionnaires are thoughtfully designed[177] and if statistical treatment of results is appropriate[1, 9] In this regard it is of interest that soft historical and hard ergometric data usually agree[1, 133, 1, 166]

The exercise test is an essential benchmark in clinical trials of antianginal therapies It provides a physiological basis for evaluation of therapy and a controlled situation which is invaluable for purposes of statistical treatment and inter institutional comparison It is important both for longitudinal assessment of individual patients and for clinical trials that the test be conducted with a progressive slowly–applied workload This method does not alter the endpoint of the test and permits greater sensitivity in detection of true but small differences[11, 1] High initial workloads may alter the endpoint of the test[21] The usefulness of exercise testing in clinical practice is not limited to diagnosis It provides a controlled situation selectively free from influence by the current events of the patient s life and may be useful in differentiating the effects of these from progression of disease It may be of help in deciding whether a patient may return to particular physical activities including a strenuous occupation The use of exercise testing in conjunction with physical conditioning programs has already been discussed Finally objective documentation of improvement is often of substantial psychological benefit to the patient

Medical failures

In certain situations it is unarguable that medical therapy of angina has failed for example the occurrence of myocardial infarction of continued clearly debilitating angina or progression of stable angina to the intermediate coronary

Table II Hemodynamic changes during exercise before and after physical conditioning in anginal patients compared with propranolol nitrate therapy

Parameter	*Untrained*	*Trained*	*Propranolol Nitrate*
HR	↑ ↑	↑	↑
SAP	↑ ↑	↑	↑
CO	↑ ↑	↑	↑
dp/dt	↑ ↑	↑	↑
LVEDP	↑	↑	↑

↑ ↑ = large increase ↑ = smaller increase HR = heart rate SAP = systemic arterial pressure CO = cardiac output dp/dt = rate of rise of systolic pressure LVEDP = left ventricular end-diastolic pressure

and may increase the subendocardial perfusion pressure [37] Propranolol increases subendocardial perfusion probably by increasing the duration of diastole From inspection of these effects, one may conclude that there are no competing beneficial actions, and that propranolol and nitrates may have additive beneficial effects on subendocardial perfusion For example the combination should both increase diastolic time and decrease diastolic wall tension The effects of each class of agent on different components of coronary vascular resistance and the ultimate importance if these effects themselves are poorly understood Here only speculation is possible

The clinical use of combined propranolol and nitrate therapy does not significantly differ from the use of either alone except perhaps in its results Nitrates do not usually prevent clinically significant propranolol induced congestive heart failure, nor do they affect the usefulness of the resting or exercising pulse rate as a guide to the degree of beta blockage Propranolol might interfere with maximal nitrate therapy by reducing the tachycardic response to hypotension, but in our experience this is not often a problem If it is we maintain the propranolol dosage at the expense of the nitrate regimen

Physical conditioning

Since physical conditioning improves exercise tolerance in normal subjects, it should not be surprising that it also does so in patients with ischemic heart disease,[88, 160, 164] although no improvement may occur if insufficient exercise is done to produce conditioning,[165, 166] and improperly performed exercise may be harmful

The hemodynamic concomitants of exercise before and after physical training in anginal patients are summarized in Table II The effects of propranolol–nitrate therapy are included for comparison Physical conditioning attenuates the effects of exercise—on heart rate, cardiac output, and myocardial contractility As a result of this improved circulatory efficiency, the MVO_2 (as determined from non invasive indices) at a given workload increases less in a trained subject permitting greater activity without the development of angina The chronic effects of conditioning are approximately equal in antianginal potency to the acute effects of nitroglycerin [160] Increased plasma fibrinolytic activity during exercise may retard the development of atheromata [27] There may be a reduction in frequency of premature ventricular beats [167] It is important to note that although reduction in cardiac death has been reported in normal persons and in patients with coronary heart disease[168] who engage in vigorous exercise, the statistical validity of most of these studies has been challenged [169] Hence, the proven benefits of exercise training as all other current therapies for coronary artery disease except perhaps beta blockade,[170, 171] are limited to symptomatic improvement

The beneficial effects of physical training are at least partially[27] due to alterations in peripheral hemodynamics Greater oxygen extraction by skeletal muscle[164] probably due to alterations in oxidative enzyme activity[172] allows decreased blood flow at a given work load [173] Probably as a consequence of this, plasma catecholamine levels during exercise are reduced in conditioned subjects [174] No direct cardiac effects of conditioning have been conclusively documented in man, although animal experiments suggest increased collateral vessel formation [175] Coronary blood flow and myocardial oxygen consumption during atrial pacing are not affected Coronary arteriograms in man are unchanged [161] It has been suggested[163] but not confirmed[161] that left ventricular performance is enhanced as a result of conditioning Favorable alterations in regional myocardial blood flow to ischemic areas has been proposed [7] but not proven

Clinical experience demonstrates that the effects of physical conditioning are additive to those of drugs Another important interaction is that an effective drug treatment program may be necessary in order to permit patients to participate in a physical training regimen Especially in

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syndrome Often, however, failure of medical therapy is a highly subjective and individual judgment A patient who desires to return to a job which demands heavy physical exertion may be unacceptably incapacitated at a functional level which many anginal patients do not even dream of achieving Another patient in the same position may be able to assume a more sedentary occupation, and may be satisfied with therapy which allows him to resume doing odd jobs at home Still other patients become cardiac neurotics and deny themselves activities which they are physiologically capable of undertaking

In the broadest sense the goal of medical therapy of angina is to return the patient to a functional status which is satisfactory to him Since no currently available treatment is clearly capable of prolonging the life span of patients with coronary artery disease, this consideration is, regrettably, irrelevant The preconceptions of the physician concerning the patient s goals should be a lesser consideration

In many instances medical failure is an indication for cardiac catheterization, and for coronary artery surgery if surgery holds reasonable promise of success This is an appropriate consideration in debilitating or unstable angina or in the patient who desires to be free of angina and is willing to accept the risks of operative morbidity and mortality and of surgical failure

When the indications for surgery are less clear, or when coronary angiography demonstrates surgically incorrectable disease, the patient s status and current medical regimen should be meticulously reviewed Weight reduction may be more attainable, or compliance with drug therapy increased, when there is no alternative Exercise testing may reveal a disparity between resting and peak exercise heart rate which provides a rationale for more aggresive propranolol therapy A carotid sinus nerve stimulator may be considered [7] In the case of the cardiac neurotic or the patient whose economic problems are paramount the help of a psychiatrist or a social worker may be invaluable It is in this situation where the proper course of action is unclear and current therapy unsuccessful that the physician s medical skill and his ability to communicate with his patient are most severely taxed

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Management of shock following acute myocardial infarction Part II Mechanical circulatory assistance

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Several years have elapsed since the introduction of mechanical circulatory aids in the treatment of shock following acute myocardial infarction We will attempt to summarize the effects of mechanical circulatory support its usefulness in clinical conditions and probable future directions of its applications

Historical aspects

In 1953 Kantrowitz and Kantrowitz[1] demonstrated an increase in the total coronary flow of dogs by increasing aortic pressure in diastole by mechanical retardation of the aortic pressure pulse Initially counterpulsation of blood was utilized to provide mechanical assistance to the myocardium with diminished coronary flow and severe dysfunction This augmented coronary flow in diastole by raising diastolic pressure and reduced pressure work of the left ventricle in systole by lowering aortic systolic pressure [2] This has the obvious rationale of unloading the left ventricle and favorably altering the myocardial supply-demand relationship Counterpulsation of blood though possessed of an attractive rationale required large bore cannulation of both femoral arteries In addition our own experiments indicated that the effects of counterpulsation of blood varied with the level of arterial pressure normal systolic arterial pressure being reduced to a much greater extent than an initially depressed arterial pressure When central aortic counterpulsation of blood was performed during profound hypotension there was only slight and inconsistent improvement of the hemodynamic abnormalities and anaerobic myocardial metabolic abnormalities associated with acute myocardial infarction and shock However when during central aortic counterpulsation an adequate central aortic pressure was maintained by phased or non phased balloon obstruction of the lower abdominal aorta anaerobic myocardial metabolic abnormalities were reversed and there were significant elevations of cardiac output coronary perfusion pressure and coronary flow with only slight increment of myocardial oxygen consumption [3]

Balloon aortic counterpulsation was originally introduced by Moulopoulos and associates with essentially the same rationale as the earlier blood counterpulsation Subsequent investigation by a large number of investigators including Clauss and associates[2] and Kantrowitz and associates demonstrated the advantages and practicality of this technique in humans with a variety of causes of diminished coronary flow and left ventricular failure and this is the technique most widely applied at present It became apparent that intraaortic balloon counterpulsation was more effective than central aortic blood counterpulsation in reversing the hemodynamic abnormalities of shock following acute myocardial infarction and was more feasible to apply to a critically ill patient The efficacy of the method in shock following acute myocardial infarction is probably more dependent on increasing a critically reduced coronary perfusion pressure and flow than in mere reduction in left ventricular work which may not achieve significant proportions when there is marked hypotension Although in general

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Balloon aortic counterpulsation was originally introduced by Moulopoulos and associates[4] with essentially the same rationale as the earlier blood counterpulsation Subsequent investigation by a large number of investigators including Clauss and associates[2] and Kantrowitz and associates[5] demonstrated the advantages and practicality of this technique in humans with a variety of causes of diminished coronary flow and left ventricular failure and this is the technique most widely applied at present It became apparent that intraaortic balloon counterpulsation was more effective than central aortic blood counterpulsation in reversing the hemodynamic abnormalities of shock following acute myocardial infarction and was more feasible to apply to a critically ill patient The efficacy of the method in shock following acute myocardial infarction is probably more dependent on increasing a critically reduced coronary perfusion pressure and flow than in mere reduction in left ventricular work which may not achieve significant proportions when there is marked hypotension Although in general

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left ventricular filling pressure is reduced by the use of intraaortic balloon pumping in experimental cardiogenic shock, this does not occur invariably and coronary flow is not invariably increased by this device despite raising central aortic diastolic pressure This probably is due to peripheral adjustments in the coronary circulation during the myocardial ischemia of the shock state which may provide maximal dilatation, reversed to some extent when coronary flow is more adequate Nevertheless, the technique generally achieves some favorable hemodynamic and cardiac metabolic alteration when used in clinical acute myocardial infarction and shock, similar in direction to experimentally obtained results in animals

Clinical studies

Reported results of the efficacy of intraaortic balloon pumping in shock following acute myocardial infarction have varied widely after initial enthusiastic reports of its therapeutic potential in this syndrome[5] Survival has been reported to vary from 11 per cent[6] to a most optimistic 71 per cent[7] Obviously to account for these enormous differences in reported efficacy of balloon pumping we must conclude that differences in criteria for the definition of 'shock' underlie the results Where 'shock is rather rigidly defined to include marked hypotension, 90 mm Hg or below, with the concomitant clinical signs of shock, the results are less good than when the definition of shock is more loosely applied with regard to systolic arterial pressure Analysis of reported series indicates that this is indeed the case Willerson and associates[6] report two reasonably long term survivors in 20 patients with acute myocardial infarction and shock undergoing intraaortic balloon pumping Both of these had acute inferior infarction The authors criteria for shock' included systolic arterial pressure of less than 85 mm Hg In contrast, Lefemine and associates[7] reported survival in 10 of 14 patients with cardiogenic shock following acute myocardial infarction A systolic pressure of less than 90 mm Hg was used as a criterion for shock' However, they report that in five patients the blood pressure was raised above 90 mm Hg by pressor agents prior to insertion of the balloon and they state that most of the group had associated findings of oliguria, peripheral vasoconstriction and diaphoresis implying that some did not It would appear that they were treating less severe instances of left ventricular dysfunction O'Rourke and associates[8] report nine patients surviving of 25 treated with the intraaortic balloon In their study, shock rigidly defined was not successfully treated but when the definition of shock was 'modified' requiring that systolic arterial pressure be less than 100 mm Hg survivals as indicated above were obtained Hagemeijer and colleagues[9] demonstrated survival in six of eight patients with left ventricular failure and in seven of 17 patients with 'cardiogenic shock, but left ventricular filling pressures are not indicated and patients over 65 years of age were excluded, as were those with ischemic episodes within 36 hours prior to pump support and, at least in some shock of more than 6 hours duration Johnson and associates[10] reported eight of 18 surviving cardiogenic shock treated with the intraaortic balloon pump without surgery The definition of shock included systolic arterial pressure below 100 mm Hg One survivor was subsequently shown to have had normal coronary arteries The authors contrast this with their previous experience with medically treated patients, showing a 7 per cent survival but it is not clear that the definition of shock was identical in the two groups Survival was more likely in inferior infarction, whereas those who survived intraaortic balloon pumping with anteroseptal infarction remained severely disabled Less sanguine results were reported by Scheidt and co workers[11] in a cooperative study involving 87 patients from several institutions, in which a 17 per cent survival rate was indicated employing a more rigid definition of shock Our own results at Mt Sinai Hospital New York are more in keeping with those of Willerson and colleagues previously cited,[6] with one or perhaps two reasonably long term survivors in 32 consecutively studied patients with acute myocardial infarction and shock rigidly defined (pressure of 90 mm Hg or below in systole with concomitant signs of shock) We excluded patients with surgically remediable ventricular septal rupture or mitral regurgitation and those in whom the shock could reasonably be ascribed to marked bradycardia tachycardia or acute myocardial ischemia

The largest series of patients to date has been studied over a period of several years by the Massachusetts General Hospital group and their findings have been published in several reports[12]

At this writing they have studied about 140 patients Analysis of 36 survivors from 120 patients (which included patients with surgically remediable ventricular septal defect and mitral regurgitation) includes 24 surviving after balloon pump support and surgery and 12 surviving with balloon support alone[13] No patient requiring balloon support with acute mitral regurgitation or ventricular septal rupture survived without surgery No survivor showed previous transmural infarction Fifty per cent of the survivors in the pump and surgical group had ventricular septal rupture or mitral regurgitation All other survivors showed some correctable abnormality contributing to the depth of shock, including resistant arrhythmias conduction abnormalities pulmonary edema and hypoxemia new ischemia and drug related myocardial depression All the non surgical survivors were stabilized by the balloon pump within 24 hours and were independent of the balloon within 4 days In the 50 per cent of the surgical survivors without ventricular septal rupture or mitral regurgitation all but one stabilized within 24 hours but all remained balloon dependent

The use of surgery to correct ventricular septal rupture or massive mitral regurgitation may add to the salvage rate as well on occasion myocardial revascularization and infarctectomy and aneurysmectomy but the mortality rate remains high well over 50 per cent and is considerably higher if the surgery must be performed within the first two weeks of the acute infarction It is beyond the scope of this paper to discuss full details of patient selection and results of the few series reported in which surgery has been performed in cardiogenic shock but it is recognized that the intraaortic balloon pump provides a useful adjuvant as circulatory support to stabilize the patient and permit appropriate hemodynamic measurements and angiography so that a decision as to the advisability and feasibility of cardiac surgery can be made It is of most benefit in this regard and has the strongest rationale in suspected ventricular septal rupture and/or mitral regurgitation By lowering the resistance to ventricular ejection the shunt across the ventricular septal defect as well as the degree of mitral regurgitation should be diminished

Before considering the precise role of intraaortic balloon pumping in specific clinical situations it is appropriate to examine the reported complications of the technique Here again reported incidence varies widely Of course this may be due to differences in the stage of surgical training of those who perform the insertion of the balloon One would logically expect fewer local complications where experienced surgeons insert the balloon in contrast to institutions where surgical residents in various stages of training perform the procedure O Rourke and associates detail eight significant complications in 30 patients (one leg ischemia one wound infection five femoral arterial thrombi and one small aortic dissection) some of which were long lasting or apparently life threatening Lefemine and associates[7] report a 17 per cent complication rate in 86 patients with intraaortic balloon insertion and failure of passage through the iliac or femoral artery in 13 per cent In some of these the balloon could be inserted through an aortic arch graft However the complication rate was 50 per cent in patients with cardiogenic shock Complications included femoral arterial obstruction requiring balloon removal iliac arterial obstruction ischemic necrosis of the calf gangrene of one or both legs aortic dissection and cardiac tamponade thought to be secondary to anticoagulation Four patients had permanent damage to the legs due to ischemia and one required bilateral amputation Serious arterial obstruction occurred in 10 per cent and there was one fatal complication (pericardial tamponade) Curtis and associates[14] report a 26 per cent complication rate in 34 patients including arterial insufficiency necessitating amputation opposite extremity embolus deep vein thrombosis groin infection groin hematoma and arterial insufficiency not requiring surgery Nine per cent of patients in the series required surgical intervention because of the complications Our own group has experienced a much lower significant complication rate Perhaps this is attributable to one senior surgeon assuming continued responsibility over the course of several years for the surgical management of intraaortic balloon insertion At any rate the possibility of significant complications particularly in patients with cardiogenic shock must be considered in arriving at a decision as to the use of the intraaortic balloon

When shall the intraaortic balloon be used?

I think the answer to this question at present should be earlier than we are currently using it

It is still not entirely clear that many lives are saved for the reasonably long term by the use of the balloon in acute myocardial infarction once the shock syndrome has developed although in general temporary hemodynamic benefit can be effected Our own studies and those of others, previously cited would support a pessimistic view as to its potential for saving large numbers of lives in cardiogenic shock Our investigation of 663 consecutive patients with acute myocardial infarction admitted to Mt Sinai Hospital New York, in an 18 month period showed a 4 2 per cent incidence of shock, reasonably rigidly defined (systolic arterial pressure below 90 mm Hg with concomitant clinical signs of shock, not attributable to hypovolemia arrhythmias, or surgically remediable ventricular septal rupture or mitral regurgitation)[15] This low incidence (4 2 per cent compared to 10 to 15 per cent in previous studies) is attributed to probable prevention of shock by more intensive treatment of pre shock conditions of congestive heart failure without shock arrhythmias, fluid deficits, and metabolic abnormalities This leaves a residuum of patients with extensive acute and old myocardial infarction refractory to all treatment for the most part The average age of these patients was 68 years Only 2 4 per cent of the patients with acute infarction exhibited the shock syndrome and were less than 70 years of age Ten patients (35 per cent of the group with shock 1 5 per cent of those with acute myocardial infarction) were less than 65 years of age There were only nine patients in an 18 month period who were less than 70 years of age and lived at least two hours after admission (a minimal time necessary for attempting emergency medical therapy and rendering the balloon pump operative) This was 1 4 per cent of our patients with acute myocardial infarction Of 14 patients subjected to intraaortic balloon pump support and emergency revascularization surgery in some there were no survivors Subsequently in a total of 30 patients with intraaortic balloon pumping for cardiogenic shock we have obtained one or perhaps two patients with reasonably long term survival If we project the salvage rate of the largest series of patients studied to date predicted salvage from intraaortic balloon pumping alone would be one or two patients in an 18 month period Predicted salvage from intraaortic balloon pumping plus revascularization and/or infarctectomy or aneurysmectomy would be about three patients in this interval, assuming an age "cut off" of 70 years From these results, it would appear that once the shock syndrome has developed unless it is attributable to a surgically remediable cause it is still associated with an extremely poor prognosis regardless of pharmacologic mechanical or surgical therapy, although a few patients may be salvaged with the intraaortic balloon One cannot apply data derived from treatment with the intraaortic balloon on the patient with severe left ventricular failure without shock to those with shock The medical therapy of those with left ventricular failure not in shock (or with rather loosely defined shock) is considerably more effective than in those with shock There is no satisfactory randomized study establishing a higher rate of survival in patients in left ventricular failure without shock treated with balloon pump support as compared to rigorous medical therapy although the use of balloon pump support in such patients has an attractive rationale The superiority or necessity of balloon pumping in the group without shock has not been established since there is a better prognosis than in the shock group when treated medically

Our current approach is to offer the intraaortic balloon pump to patients in shock generally less than 70 years of age who do not respond to pharmacologic attempts to raise arterial pressure and to treat congestive heart failure and significant arrhythmias within a short period of time The possible hazards of the procedure and poor prognosis with balloon pump support must be explained carefully to the patient and family Patients who deteriorate on the balloon are not studied further Those who are balloon dependent after a few days have coronary arteriography and left ventriculography performed and a recommendation made on this basis whether a surgical approach is warranted The criteria for the latter are not precise but generally revolve around adequacy of some left ventricular function presence or absence of a discrete aneurysm and bypassable coronary arterial obstructions Of course those with ventricular septal rupture or high degree mitral regurgitation are offered surgery, as late as possible after the acute myocardial infarction, depending on clinical stability For those who can be weaned from the balloon many advocate early angiographic study (with the balloon operative) My own preference has been to defer these procedures unless there is

thought to be a ventricular septal rupture or mitral regurgitation because of the high degree of surgical risk in performing coronary bypass surgery infarctectomy or aneurysmectomy early after acute myocardial infarction

A question frequently asked is whether a community hospital without cardiac surgical or angiographic facilities should offer balloon pumping to its patients This is not answered easily but from our own figures predicted salvage would be quite low for the patient in shock and therefore the number of patients so benefited would be very small Of course the balloon pump may be used for other purposes on occasion such as refractory ventricular tachycardia or recurrent severe myocardial ischemia but here too the number of patients benefited would be small It would appear more rational for such institutions to group their efforts so that perhaps each region might have a balloon pump available

Future trends

Because of dissatisfaction with current survival rates with the balloon pump once the shock syndrome has developed it is reasonable to explore other modalities of circulatory support or the use of the balloon pump in pre shock states in an effort to prevent the shock syndrome There has been considerable investigation of the concept of preservation of ischemic myocardium and indeed infarct size as judged by ST segment elevation and CPK release from the myocardium can be reduced by intraaortic balloon pumping in an experimental setting [6] Whether or not intraaortic balloon pumping can prevent shock in humans with acute myocardial infarction has not been determined but it is accepted that the shock syndrome is associated with extensive left ventricular infarction both old and recent in various stages of development so it is conceivable that preserving ischemic myocardial tissue may prevent critical degrees of necrosis leading to the shock syndrome As a practical matter it is unlikely that the technique will be applied to good risk patients because of the possible complications of the procedure and the acceptable prognosis without balloon pumping However hemodynamic subsets have been defined with accompanying prognoses It would appear most rational to apply the intraaortic balloon pump to those patients not in shock who have severe left ventricular dysfunction and a poor prognosis but this should be studied in a careful randomized manner so that appropriate conclusions can be drawn as to the efficacy of the balloon in preventing the development of shock and improving the eventual prognosis Such data are not available at this time

Other techniques of circulatory support may be useful in the future but none has been tested sufficiently to have established itself as superior to the intraaortic balloon External counterpulsation has the advantage of a non invasive technique and hence should avoid the vascular complications of the intraaortic balloon Although there is some evidence that the myocardial supply–demand ratio may be favorably affected by this technique [1] hemodynamic studies have shown much less reduction of the elevated left ventricular filling pressure in acute myocardial infarction with severe left ventricular dysfunction when extracorporeal counterpulsation is employed than when intraaortic balloon pumping is utilized A recent cooperative trial of external counterpulsation was reported to be of benefit in reducing the mortality rate of patients with clinical Class II acute myocardial infarction (mild congestive heart failure) However in this study investigating a group with relatively good prognosis no hemodynamic measurements were obtained in the treated and untreated groups so that accurate assessment of the efficacy of the device is not possible It is unlikely however that the extracorporeal technique will be of sufficient efficacy to affect the clinical course of the patient already in shock but it is possible though by no means established that it may be of prophylactic benefit in certain hemodynamic subsets

Techniques of left ventricular bypass are more effective in unloading the failing left ventricle than is the intraaortic balloon pump and such techniques may be helpful in reversing and preventing ventricular fibrillation in acute myocardial infarction [19] Long lasting and effective left ventricular bypass in postoperative patients with open chest cannulation of the left atrium and aorta has been obtained by Litwak and associates [20] Other left ventricular assistance devices are being studied and it is probable that relatively long term left ventricular bypass will be feasible and effective In instances of severe left ventricular dysfunction due to acute myocardial infarction unresponsive to medical measures and intraaortic balloon pumping prolonged and effec

tive circulatory support may be possible following open chest aortic and left ventricular or left atrial cannulation

Conclusions

Intraaortic balloon pumping may provide temporary hemodynamic benefit in acute myocardial infarction with shock but reports have differed rather widely concerning its efficacy in providing long term survival Much of this variation depends on differing criteria for the definition of shock " Low survival rates are obtained when the syndrome is rigidly defined, but rates are considerably higher when patients with systolic arterial pressures higher than 90 mm Hg are included The intraaortic balloon is of considerable efficacy in stabilizing the patient with a surgically remediable cause for the shock syndrome, such as ruptured interventricular septum or massive mitral regurgitation Survival rate is low even with the intraaortic balloon when shock is present in the absence of such conditions, although there may be slight additional salvage with emergency revascularization and/or infarctectomy and aneurysmectomy

The complication rate of intraaortic balloon insertion is not inconsiderable with some studies showing about a 17 per cent incidence but with a much higher rate (as much as 50 per cent) in patients with cardiogenic shock These include arterial insufficiency of the lower extremities, infection, hemotomata occasionally dissection of the aorta, and arterial occlusions necessitating amputations Death due to the procedure is quite rare

It is not clear whether the balloon pump improves survival in patients with severe left ventricular failure who are not in shock and do not have ruptured interventricular septum or advanced mitral regurgitation because the medical management of such patients provides much better results than it does in patients with shock It would be necessary to perform studies of randomized patients with and without circulatory support in these hemodynamic subgroups to determine the true efficacy of the balloon pump in patients with severe heart failure but not in shock

Analysis of the patient population with shock following myocardial infarction indicates that the incidence of shock is declining probably because of better methods of treating congestive heart failure, arrhythmias, and metabolic derangements The average patient is of advanced age with a history of previous myocardial infarction The number of patients who reasonably can be expected to survive because of intraaortic balloon pumping is small once the shock syndrome has developed

Because of the poor results with all modalities of treatment once the shock syndrome is apparent, attention should be directed to attempts to prevent shock and to other means of circulatory support It is not known whether shock can be prevented but use of the intraaortic balloon pump in poor risk patients who are not in shock as determined by hemodynamic measurements should be studied intensively for this purpose Techniques of left ventricular bypass to provide long lasting circulatory support may be fruitful in reducing mortality in patients with cardiogenic shock or in those with severe left ventricular failure

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Special report

Definition of terms related to cardiac rhythm

WHO/ISC Task Force*
Utrecht The Netherlands and New York N Y

In recent years several individuals and working groups have been concerned with definition and classification of electrocardiographic findings Several factors notably increasing international communication, exchange of data and introduction of new techniques like computer aided interpretation of the electrocardiogram have promoted the need for common language in electrocardiology

A joint initiative of Dr E Dekker, Medical Director of the Dutch Heart Foundation (DHF) and Dr Z Pisa Chief Cardiovascular Diseases of the World Health Organization (WHO) resulted in an international Task Force composed of members of various cardiological societies Sponsored by WHO and the International Society of Cardiology with financial support from the Dutch Heart Foundation (DHF) this working group has been concerned primarily with the definition of terms related to cardiac rhythm The results are presented in the format of a glossary arranged in alphabetical order and composed of two sections The first part consists of acceptable terms and synonyms while in the second part a list of non preferred terms is given (NPT) Reasons for discouragement and preferable synonyms have been given With few exceptions, only those terms have been defined that are commonly used in clinical electrocardiography and clinical electrophysiology and which have bearing on the classification of arrhythmias Many terms which primarily relate to anatomical structures and basic electrophysiological events have not been defined

Definitions are given in general terms preferably with their specific electrocardiographic meaning Since quantitative data may be related to special circumstances like age, technique of recording etc, they have when possible, been avoided Likewise mechanisms of arrhythmias have not been included in the definitions of specific disorders of rhythm although some of them have been considered separately

While the committee realizes the need for updated specifications of recording equipment it considers this aspect beyond the scope of its assignment

This report as a draft served as a working document for Task Force I of the tenth Bethesda Conference on Optimal Electrocardiography of the American College of Cardiology (ACC) Several amendments of the ACC group have been incorporated in our report and care has been taken to avoid major inconsistencies in the terminology of the two groups

LIST OF ACCEPTABLE TERMS & SYNONYMS

Aberrant conduction

The abnormal spread of an impulse through the normal or expected pathway resulting in an altered ECG wave form Aberrant conduction may occur in the ventricles or within the atria In cases of altered intraventricular conduction of supraventricular impulses it is preferred to reserve the term for conduction over the normal

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pathway thus excluding conduction over accesso ry pathways as in the Wolff Parkinson White Syndrome (WPW) Furthermore use of the term aberrant conduction only seems meaningful if a rate related or other functional mechanism underlies the altered spread of excitation

Abortive re entry

See *re-entry*

Accelerated rhythm

Three or more consecutive impulses occurring at a rate of less than 100/min but greater than the inherent rate of that pacemaker In each case the rate and site of impulse formation should be indicated (See also *inherent rate*)

Advanced (second degree) block

A form of second degree block in which alternate or two or more consecutive impulses fail to be conducted Thus advanced block encompasses 2 1 3 1 4 1 block etc (See *second and third degree block*)

Alternating rhythms

Impulse formation at two or more different sites in which one rhythm alternates with the other Each rhythm should be specified sepa rately e g sinus rhythm alternating with parox ysmal atrial fibrillation or sinus rhythm alternating with episodes of accelerated ventric ular rhythm in which the latter is conducted retrogradely to the SA node (See also *dual multifocal and multiple rhythm*)

Anterograde (orthograde) conduction

Conduction of a cardiac impulse in a forward direction e g from the atria or atrioventricular (AV) junction to the ventricles Anterograde indicates a directional movement and is therefore preferred over antegrade in which ante denotes a forward position as in antechamber (See also *retrograde conduction*)

Arrest

Cessation of electrical activity of the heart or part of it Arrest may be caused by different electrophysiological mechanisms Although not always possible it is desirable to distinguish arrest from the pause in manifest electrical activ ity caused by exit block

Arrhythmia

Any cardiac rhythm other than normal sinus rhythm Such a rhythm may be either of sinus or ectopic origin and either regular or irregular An arrhythmia may be due to a disturbance in impulse formation or conduction or both It is preferred to use the term arrhythmia only as a general heading and not as a synonym for irreg ular impulse formation Thus use of the term sinus arrhythmia is discouraged *It seems* better to characterize a rhythm by the adjectives regular or irregular For the same reason the term tachy arrhythmia should be avoided

Atrial dissociation

A dual atrial rhythm in which two simulta neously active pacemakers do not affect each others activity or rhythmicity (See also *dual rhythm*)

Atrioventricular (AV) block

The independent activation of atria and ventri cles by differently originating impulses Activa tion of the atria may arise from the SA node the atria or the AV junction while ventricular activa tion arises from the AV junction or the ventricles Dissociation may occur for single activations or it may last longer In the presence of captures dissociation is *incomplete* When there are no captures during the time of recording dissocia tion is considered to be *complete* AV dissociation is a descriptive term which does not obviate the need to look for the underlying mechanism(s) It should not be used as a synonym for complete AV block which may be one of the underlying mech anisms of AV dissociation (See also *dual multi focal and multiple rhythm and parasystole*)

Bigeminy

A repetitive pattern of two relatively closely spaced activations usually followed by a longer interval Several mechanisms—which should be specified if possible—may underlie bigeminy In its most common form the second impulse of the pair is an extrasystole (extra systolic bigeminy) (See also *trigeminy*)

Block

Delay or failure of impulse propagation

Varying degrees of conduction disturbance may occur anywhere in the heart in both the antero

grade and retrograde directions (See also *entrance and exit block AV and VA block, first, second and third degree block*)

Bradycardia

Three or more consecutive impulses from the same pacemaker at a rate less than the lower limit of its inherent rate (See also *accelerated rhythm and tachycardia*)

Bundle branch block (BBB)

Delay or failure of condition within a bundle branch BBB may be complete, incomplete permanent or intermittent (nonpermanent)

Bundle branch block complete (CBBB)

CBBB indicates either absence of conduction in a bundle branch, or delay of such magnitude that ventricular activation occurs largely or exclusively through the contralateral bundle, this causes widening of the QRS complex to 0 12 seconds or more

Bundle branch block incomplete (IBBB)

IBBB indicates delay in activation of a ventricle resulting from delayed conduction within the ipsilateral bundle branch The involved ventricle may be partially activated by the impulse from the contralateral bundle

Bundle branch block intermittent (nonpermanent)

This indicates intermittence of a BBB pattern (See also *aberrant conduction and permanent BBB*)

Bundle branch block permanent

A BBB pattern which is always present and at all heart rates

Capture

Usually premature activation of either the atria (atrial capture), by a retrogradely conducted ventricular or junctional impulse, or of the ventricles (ventricular capture), by an anterogradely conducted supraventricular impulse Captures are most commonly seen during episodes of AV dissociation They should be distinguished from other types of premature impulses (See also *extrasystole*) The occurrence of a capture at a time when the atria or ventricles have already been partially activated by another pacemaker impulse results in a *mixed or fusion complex,* also called *partial or incomplete capture* (See *fusion complex*)

Cardiac electrogram (CEG)

A uni or bipolar record of electrical activity of the heart, taken with the electrode(s) within a cavity of the heart or in contact with the myocardium (direct leads) e g intracavitary EG, epicardial EG, etc

CEG's can be further defined according to the position and proximity of the recording electrodes to a given structure Thus, intracavitary electrograms may be recorded from the right or left atrium (high or low), from the region of the atrioventricular (AV) junction (AV junctional EG), from the ventricles etc

An AV junctional EG may be labelled a *His bundle electrogram* (HBE) when a His bundle deflection is recorded If this is not the case, the record should be called an *A V junctional EG* (See also *electrocardiogram*)

Complete block

See *third degree block*

Concealed conduction

Partial penetration of an impulse into the AV conduction system or a pacemaker-myocardial junction, which exerts an influence on subsequent impulse formation or conduction, or both

In a surface ECG lead the penetration of a blocked impulse into a specific structure can only be inferred from its effect on subsequent events

With intracavitary (e g an HBE) or intracellular electrograms it is sometimes possible to demonstrate penetration of the blocked impulse to the level of recording In such cases the impulse is not concealed at that level

Concealed re entry

See *re entry*

Conduction ratio

The ratio of the number of impulses that are formed to the number of impulses which are completely propagated This ratio may be constant throughout the record, or it may vary (variable conduction ratio indicating variable

degrees of block) Wherever applicable the conduction ratio should be specified

Coupling interval

The time relationship between two designated events in the cardiac cycle which are presumed to be linked (coupled) to one another This time relationship may be fixed or constant or it may vary (variable coupling) However in cases of independent rhythms (e g continuous AV junctional or ventricular parasystole with retrograde block of parasystolic impulses) when the activity of neither pacemaker is linked to that of the other the term varying coupling inter val to denote variable intervals between ac tivations from the two pacemakers is inappro priate

Designation of cardiac electrogram deflections

Deflections in the CEG are labelled according to the electrical activity they are presumed to represent

SAN = sinoatrial nodal deflection
AVN = atrioventricular nodal deflection
A = atrial deflection
H = His bundle deflection
V = ventricular deflection
RB = right bundle branch deflection
LB = left bundle branch deflection

Recordings of SA and AV nodal activities have not been universally accepted

Designation of electrocardiographic deflections

P = atrial activation
QRS = ventricular activation
ST T = ventricular repolarization
U = origin uncertain possibly terminal phase of Purkinje fiber repolarization

Dual (double) rhythm

The *simultaneous* and *independent* occurrence of two rhythms Simultaneous activity of two pacemakers implies that the one with the slower rate of discharge is protected against the impulses of the faster one The protection can be located within the pacemaker-myocardial junction (as in parasystole) within the myocardium (as in atrial dissociation) or within the AV conduction system (AV dissociation) Each rhythm should be speci fied separately (See also *alternating multifocal and multiple* rhythm)

Echo

Return of an impulse to its chamber or area of origin This results in an atrial or ventricular echo respectively The reentrant pathway may be within the chamber of origin or other portion of the heart (See *reciprocal or re entrant impulse*)

Electrocardiogram (ECG)

A uni or bipolar record of electrical activity of the heart taken with the electrodes outside a cardiac cavity and not in contact with the myocardium (surface or indirect leads) e g esophageal ECG body surface ECG If His bundle activity is recorded with *body surface* leads this should be called a His bundle ECG (See also *cardiac electrogram*)

Entrance block

Delayed *or failed* penetration of an impulse into a pacemaking center When an impulse fails to penetrate and reset (discharge) a pacemaker the latter is said to be protected When there is delayed or only occasional resetting protection is incomplete (See also *exit block*)

Escape (impulse or discharge)

Up to two consecutive impulses (SA nodal atrial AV junctional or ventricular) arising from the *same* or occasionally from different pace maker(s) as a result of undue delay in the formation or arrival of the expected impulse of the prevailing rhythm (See also *escape rhythm and premature impulse*)

Escape *rhythm*

Three or more consecutive escapes

Exit block

Delay or failure of an impulse to reach or discharge the myocardium surrounding a pace maker This definition also applies to sinoatrial conduction (See also *entrance block*)

Extrasystole

A premature impulse which usually shows a fixed (and *probably* causal) relationship to the preceding activation of the *same* cardiac cham ber Extrasystoles may also be induced electrical ly *or mechanically* in such cases a causal rela tionship to the *preceding* activation is usually

grade and retrograde directions (See also *entrance and exit block AV and VA block, first second and third degree block*)

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Concealed re entry

See *re entry*

Conduction ratio

The ratio of the number of impulses that are formed to the number of impulses which are completely propagated This ratio may be constant throughout the record or it may vary (variable conduction ratio indicating variable

where the premature complex arises The conduction time of the impulse immediately following the premature discharge is usually prolonged due to concealed conduction of the premature impulse

Intervals in the cardiac electrogram (CEG)

Since the technique of recording a CEG may differ it is necessary to indicate whether a uni or bipolar lead was used the inter electrode distance the filter frequency used the frequency response of the recording equipment and the points at which interval measurements are made If under specific circumstances the intrinsic deflection is used in measuring intervals in CEG s this should be clearly stated Normal values should be given for each laboratory

PA from the earliest onset of the P wave in any of the simultaneously recorded ECG leads to the onset of A in the CEG (HBE)

PH from the earliest onset of the P wave in any of the simultaneously recorded ECG leads to the onset of H in the HBE

AH from the onset of A to the onset of H in the HBE

HV from the onset of H to the onset of V in the HBE

HQ HR from the onset of H in the HBE to the earliest onset of Q or R in any of the simultaneously recorded ECG leads

RB V RB Q and LB V LB Q defined in the same way as HV and HQ respectively

Intervals in the electrocardiogram

It is customary to measure these intervals in the limb leads

PQ or PR interval from the earliest onset of the P wave to the earliest onset of the Q or R wave of the QRS complex

PQ or PR segment from the end of the P wave to the onset of the QRS

P width from the onset of the end of the widest P wave

QRS width from the onset of the end of the widest QRS complex

QT interval from the onset of Q or R to the end of the T wave

Intra atrial conduction delay

Conduction delay within the atria resulting in abnormal widening and/or distortion of the P wave in the ECG

Longitudinal dissociation

The presence of dissimilar conduction and excitability properties in dual conduction pathways that have common proximal and distal common connections One pathway (β) displays a long refractory period and fast conduction velocity while the reverse holds true for the other pathway (α)

Mobitz type I block

See *second degree block type I*

Mobitz type II block

See *second degree block type II*

Multifocal (multiform) rhythm

A rhythm of either supraventricular or ventricular origin which is characterized by varying cycle lengths and morphologies of the activation waves Such a rhythm should further be specified according to the rate of impulse formation Multiform configuration of the waves may point to multifocal origin although this is not necessarily the case (See *alternating dual and multiple rhythm* and also *chaotic rhythm and wandering pacemaker NPT*)

Multiple rhythm

The *simultaneous* and *independent* occurrence of two or more rhythms e g dual (double) triple or quadruple rhythms Each of these should be specified separately (See also *alternating dual and multifocal rhythm*)

Nonspecific intraventricular block

Any type of intraventricular conduction disturbance that cannot be completely ascribed to block in the specific conduction system (See also *arborization block intramural conduction disturbance myofibrillar parietal and peri infarction block NPT*)

Orthograde conduction

See *anterograde conduction*

Pacemaker

A group of cardiac fibers initiating one or more activations This definition does not take into account the various mechanisms which may be involved in the generation of a cardiac impulse From the electrophysiological point of view the term is not restricted to an anatomically identifi

absent (See also *capture echo and premature impulse*)

Fascicular block

Fascicular block is an electrocardiographic (electrophysiologic) concept ascribed to a conduction defect in one of the fascicles of the left bundle branch (See *fascicular block anterior and posterior*) As yet the ECG pattern of block in the (mid) septal fascicle of the left bundle branch is not well known Although the concept of fascicular block proves very useful and is indeed widely accepted, precise well defined anatomical correlates have not been identified

Fascicular block (left) anterior

The ECG concept of block in the anterior fascicle of the left bundle branch as the basis of delayed activation of the anterolateral wall of the left ventricle (See also *fascicular block*)

Fascicular block (left) posterior

The ECG concept of block in the posterior fascicle of the left bundle as the basis of delayed activation of the posterior wall of the left ventricle (See also *fascicular block*)

Fibrillation

Irregular, disorganized electrical activity of atria or ventricles In *atrial fibrillation* P waves are absent and the baseline consists of irregular waveforms which continuously change in shape, duration, amplitude, and direction In the absence of advanced or complete AV block, the resulting ventricular response is totally irregular (random) In *ventricular fibrillation* QRS and T waves can no longer be identified The recorded deflections continuously change in shape duration, magnitude and direction

First degree block

Delayed conduction with a 1 1 conduction ratio In any individual case the conduction time should be specified (See also *second and third degree block*)

Flutter

Rapid and regular electrical activity of atria or ventricles which is characterized in at least one ECG lead by the absence of an isoelectric line between the deflections of the fluttering chamber

In *atrial flutter* the rate of the atria is usually in the range of 200 350/minute Some distinguish between *typical* and *atypical* forms of atrial flutter In the typical variety the tracing displays a saw tooth appearance in Leads II and III while this is not the case in the atypical form The distinction between the atypical form of atrial flutter and atrial tachycardia with a rapid rate is not always possible

In *ventricular flutter,* the ventricular rhythm is regular, the rate usually exceeds 250/minute and, the components of QRS and T cannot be identified or separated

Fusion (mixed) complex

See *capture*
Simultaneous or near simultaneous activation of either atria or ventricles (atrial or ventricular fusion complex respectively) by impulses coming from different directions This results in an electrocardiographic complex which is intermediate (mixed) in form between the deflections resulting from activation by each single impulse

Gap in conduction

A period in the cardiac cycle during which there is absence of conduction, whereas conduction occurs with impulses of greater and lesser prematurity Gap in conduction is usually seen during AV or VA transmission, but it probably also occurs in other parts of the heart

Incomplete (partial) block

Is a definition encompassing first and second degree block

Inherent rate

The frequency of impulse formation which is generally attributed to a given pacemaker localization The inherent rate may differ according to age or other factors For adults the following values are thought to be representative

SA node 50 100/min
atrium not well known probably 40 65/min
AV junction 40 60/min
ventricle 35 40/min

Interpolation

The phenomenon in which a premature impulse usually of ectopic origin occurs between two consecutive impulses of another pacemaker both of which are conducted to the chamber

in the cardiac cycle during which a premature impulse is conducted more slowly than one falling outside the refractory period (P_2 P_7 in Fig 1)

Functional refractory period (FRP) The shortest possible ventricular or atrial interval resulting from two consecutively conducted atrial or ventricular activations respectively For the anterograde conduction this interval is indicated by $QRS_{1,5}$ in Fig 1

Retrograde conduction

Conduction of a cardiac impulse in a reverse direction usually used to indicate ventriculo atrial conduction (See also *anterograde conduction*)

Second degree block

A conduction disturbance in which not every impulse is completely propagated from its site of origin The term second degree block should only be applied during sustained impulse formation Thus it should not be used in cases of non conducted premature impulses (See also *conduction ratio*)

Second degree block type I (Wenckebach) (Mobitz type I) Intermittent failure of impulse conduction in which the blocked impulse is preceded by prolongation of conduction time relative to the first conducted impulse

In the *typical variety* the increment in conduction time progressively decreases resulting in progressive shortening of the activation interval of the receiving chamber until the blocked impulse occurs This typical structure is rare but is of importance in recognizing type I exit block

Most cases of type I block involve *atypical varieties* in which the increment in conduction time varies and it is not necessarily the second impulse of the series which shows the greatest increment (See also *second degree block type II and advanced block*)

Second degree block type II (Mobitz type II) Intermittent failure of impulse propagation following a number of conducted impulses showing constant conduction times The diagnosis of type II block is supported by the finding of a similar conduction interval following the blocked impulse (See also *second degree block type I and advanced block*)

Short PR syndrome

This is a form of ventricular pre excitation in which the PR interval is shortened to less than

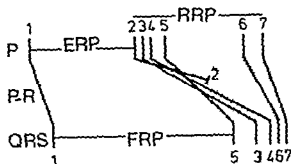


Fig 1 Diagrammatic representation of the various phases of the refractory period of the AV conduction system P 7 is the first of a series of atrial impulses which is conducted through the AV junction (PR) with the same conduction velocity as P 1 For abbreviations and definitions, see refractory period "

0 12 sec while the QRS complex usually is normal i e showing the same configuration as during a normally conducted sinus rhythm May be associated with re entrant supraventricular tachycardias It should be stressed that not all cases showing a short PR interval on the ECG are examples of ventricular pre excitation Before making such a diagnosis one should ascertain that criteria for ventricular pre excitation are fulfilled (See *Lown Ganong Levine syndrome in NPT pre excitation* and *Wolff Parkinson White pattern and syndrome*)

Supernormal conduction

Conduction which is less abnormal than would be expected not faster than normal

Supernormal excitability

Unexpected activation resulting from a sub threshold stimulus Supernormal excitability is limited to a relatively narrow interval of the cardiac cycle

Tachycardia

Three or more consecutive impulses at a rate exceeding 100/min (See also *accelerated rhythm*)

Third degree or complete block

Complete failure of impulse propagation usually associated with independent and slow activation of the chamber distal to the site of block In order to diagnose complete block one should ascertain that the opportunity for conduction to occur is present and yet transmission fails Complete block in one direction does not necessarily imply complete block in the reverse direction (See also *AV dissociation*)

able group of cells showing spontaneous phase 4 depolarization

Pacemaker ectopic or *subsidiary* any pace maker outside the sino atrial (sinus)node

Pacemaker, primary the sinus node

Terms like latent' and "potential" pace makers refer to inactive (dormant) cells having the property of pacemaking, while subsidiary *may refer to both active and latent* ectopic pacemakers A latent pacemaker may be located within the SA node itself

Parasystole

A rhythm consisting of dual activations of a single cardiac chamber, in which one pacemaker (the parasystolic focus) is protected from being discharged by the other The latter is usually responsible for the prevailing rhythm

At times two or even more parasystolic rhythms may coexist (*multifocal parasystole*) When the protection intermittently fails, the parasystolic center may be discharged by a pene trating impulse occurring at a critical time interval and parasystole is said to be *intermittent* (See also *entrance block and atrioventricular dissociation*)

Partial block

See *incomplete block*

Partial re entry

See *re entry*

Pre excitation

Excitation of part or all of a cardiac chamber earlier than if impulse propagation had occurred over the normal conduction system The mor phology of the excitation wave need not neces sarily be different from normal Anterogradely the ventricles may be pre excited and retro gradely the atria may be pre excited

The term pre excitation can also be applied in cases of artificially induced excitation, wherein mechanical or artificial stimulation occurs prior to or simultaneously with the normally con ducted impulse (See also *Wolff Parkinson White pattern and syndrome* and *short PR syn drome*)

Premature impulse (activation complex or discharge)

An activation which precedes the expected discharge of the prevailing rhythm This applies to extrasystoles, echoes, captures, and manifest activations from a parasystolic pacemaker Early ventricular activations in atrial fibrillation or flutter should not be called premature since in these arrhythmias prematurity cannot be proven

Premature impulses may occur singly or in pairs (doublets) When three or more are recorded in succession at a rate exceeding 100/min , this is by definition a (brief) *tachycardia*

A premature impulse is usually of ectopic origin

Quadrigeminy

Defined according to *trigeminy*

Reciprocal or re entrant impulse

One re entrant movement (see *echo, re entry and reciprocation*)

Reciprocation

Continued reentry (circus movement) leading to several consecutive activations of a cardiac chamber (See *re entry*)

Re entry

The phenomenon in which a cardiac impulse enters a circuit and returns *to* or *toward* its area of origin Re entry may result in one or more activations of the heart or part of it, or it may remain concealed The latter is evident from the after effect on subsequent impulse formation and/or conduction, and is called *concealed attempted partial or abortive re entry*

Refractory period

That period in the cardiac cycle during which the conduction system and the myocardium demonstrate no or an altered response to a stim ulus The various phases of the refractory period of the AV conduction system are depicted diagrammatically in Fig 1

Absolute refractory period (ARP) That period in the cardiac cycle during which the heart is not excitable At the cellular level, localized non propagated electrical activity may still be record ed In a surface or intracavitary recording, the ARP is probably identical to the ERP

Effective refractory period (ERP) That period in the cardiac cycle during which an impulse (whether premature or not) fails to conduct (P_1 P_2 in Fig 1)

Relative refractory period (RRP) That interval

tion either regular or irregular or a slow ventricular response due to advanced or complete block (See also *arrhythmia*)

Bundle branch block bilateral

Bilateral bundle branch block connotes a conduction disturbance involving both the right bundle branch and the main stem of the left bundle branch or one or both of its fascicles Like bi and trifascicular block this term serves no special purpose Instead the site degree and type of block should be specified (See also *bi and trifascicular block (LUT)*

Chaotic rhythm

This term should be avoided since it is difficult to define chaos These rhythms are best described as irregular with multiform configuration of the waves (See *multifocal rhythm*)

Depolarization

Loss of membrane potential Since this occurs at a cellular level its use is best restricted to the description of the electrophysiological phenomenon In clinical electrocardiography when referring to a deflection which represents the electrically active state of the myocardium the term is best replaced by *activation discharge excitation* or *impulse*

Fibrillo flutter

This term implies a supraventricular arrhythmia with some characteristics of atrial flutter and some of atrial fibrillation Such records are best classified as atrial fibrillation when the ECG criteria of atrial flutter are not quite satisfied It should not be mistaken for the alternation of atrial flutter and fibrillation in the same record

Hemiblock left anterior

(Left) anterior fascicular block is considered a more appropriate term (See *fascicular block anterior*)

Hemiblock left posterior

(Left) *posterior fascicular block* is considered more appropriate (See *fascicular block posterior*)

High degree block

By definition this is still a form of second degree block However since high degree (high grade) second degree block is a contradiction in terms it seems more appropriate to classify these conduction disturbances as *advanced (second degree) block*

High grade block

See *high degree block*

Idiofocal tachycardia

This term suggests a focal origin of an enhanced rhythm which may not be true in every case Furthermore as with the terms *non paroxysmal* and *slow tachycardia* which are sometimes used as synonyms objections may be raised against using the term *tachycardia* at rates below 100/min The arrhythmia should be characterized as *accelerated rhythm* or *tachycardia* with further specification according to the site of impulse formation

Interference

Rarely has a term created so much disagreement and confusion as interference Some have used it to indicate the short disturbance of the rhythmic action of one pacemaker by the activity of another (e g resetting of a junctional or ventricular pacemaker by a ventricular capture during incomplete AV dissociation) while others have defined interference as the expression of a physiological mechanism namely delay of failure of impulse conduction due to induced normal refractorinesss of a conduction pathway or the myocardium (collision of two impulses coming from opposite directions or the same direction)

Since this controversy has not yet been definitively settled if it ever will be it seems best to avoid the term for the time being There seems to be no reason to indicate emphatically that the activity of a pacemaker is disturbed by a capture as is suggested by the first definition Only when resetting does not occur may specific phenomenon (protection pasasystole) be present On the other hand in analyzing the mechanisms which are responsible for failure of impulse conduction it is convenient to separate an abnormal from a physiological cause The latter can be indicated by delay or failure of conduction due to refractoriness "

Intramural conduction disturbance

This term suggests the site of a conduction disturbance within the ventricles causing nonspecific widening and/or slurring and notching of the QRS complex In most cases however the

Trigeminy

A repetitive pattern of three relatively closely spaced activations, usually followed by a longer interval In the most common form of trigeminy, the third impulse is an extrasystole (extrasystolic trigeminy) Rarely, one may be dealing with one sinus impulse followed by two consecutive extra systoles The latter is indicated as a doublet

Ventriculo atrial (VA) block

Delay or failure of an impulse to be conducted from the ventricles to the atria (See also *retro grade conduction*)

Vulnerable period

A relatively short period in the cycles of atria or ventricles, during which activation results in a repetitive response or fibrillation The vulnerable phase of the ventricles generally corresponds to the ascending and apical portion of the T wave

Wenckebach block

See *second degree block, type I*

Wolff Parkinson White (WPW) pattern

By this is meant pre excitation of the ventricles over an additional and abnormal anatomical AV connection In such cases excitation over the accessory pathway causes shortening of the PR interval Δ waves and widening of the QRS complex

Recent knowledge indicates that values for PR interval Δ wave, and QRS width are variable For instance the PR interval may be longer than 0 12 sec and Δ waves may be small and difficult to recognize Furthermore, the ECG manifestations may be intermittent and the anatomical substrate for re entrant tachycardias may be present although undetectable on the routine surface ECG (See *pre excitation short PR syndrome and WPW syndrome*)

Wolff Parkinson White (WPW) syndrome

This implies the occurrence of re entrant supraventricular tachycardias in association with the WPW pattern (See also *pre excitation and short PR syndrome*)

LIST OF NON PREFERRED TERMS (NPT)

Accelerated conduction

Accelerated AV conduction used to be designated whenever a short PR interval (< 0 12 sec) was seen in the absence of other signs of ventricular pre excitation However true acceleration of conduction has not been demonstrated and recent knowledge indicates that pre excitation of the ventricles via an anatomical connection bypassing the AV nodal delay may result in a short PR interval and normal QRS complex or only a small Δ wave The term "accelerated conduction" is therefore discouraged Instead, a *short PR syndrome* should be diagnosed whenever circumstantial evidence supports the diagnosis of ventricular pre excitation In other cases, it seems best to just indicate a *short PR interval* not necessarily implying ventricular pre excitation and thus not identical to the short PR syndrome

Antegrade conduction

See *anterograde conduction*

Arborization block

See *intramural conduction disturbance (NPT)*

Beat

Use of this term in electrocardiographic nomenclature is inappropriate since it connotes the mechanical event following excitation of a cardiac chamber Instead, we suggest use of the terms *activation, discharge excitation* or *impulse* or more descriptively *complex deflection* or *wave* (See also *depolarization NPT*)

Bifascicular block

The term ' bifascicular block is controversial In previous terminology the right bundle branch was sometimes referred to as a bundle and sometimes as a fascicle, this is inconsistent It is preferable not to consider the right bundle branch as a fascicle Therefore use of the term bifascicular block' for the combination of right bundle branch block plus block in the anterior or posterior fascicle of the left bundle is discouraged Furthermore block occurring in two fascicles of the left bundle branch cannot usually be differentiated with certainty from main left bundle branch block Thus even in the latter setting the term bifascicular block serves no special purpose Instead the site type and degree of block should be specified (See also *trifascicular block NPT*)

Bradyarrhythmia

The term bradyarrhythmia has been used in various settings to connote slow impulse forma

Fine flutterings of the aortic valve as demonstrated by aortic valve echocardiograms

Aortic valve echocardiograms were first recorded by Edler using an excised calf heart Subsequent studies by Hernberg and associates and by Gramiak and Shah described the typical configuration of the non coronary and right coronary aortic leaflets Recently Feizi and co workers described this valve in more detail and in their report again noted the boxlike appearance of the aortic leaflets in systole and the central line during diastole The latter line could be seen as two or three echo signals with hairline separation of 1 mm or less At the onset of systole the central lines were replaced by two parallel lines lying in close proximity to the aortic root In their description they mentioned that often a very fine fluttering of the aortic valve echo was seen during systole However no attempt to ascertain the incidence or conditions under which this fluttering was observed was attempted by this group We therefore undertook to delineate further the circumstances underlying this phenomenon

Two hundred fifty consecutive echocardiograms done at the Philadelphia General Hospital non invasive laboratory between March and December 1975 were reviewed These were obtained using a Unirad ultrasonoscope with a 0 5 inch unfocused transducer emitting 1 000 pulses per second and were recorded on a DR 8 Electronics for Medicine recorder at 50 mm /sec paper speed Of these 250 echocardiograms reviewed 47 were technically unsuitable and were elimi nated

Those patients with suitable records for study ranged in age from 18 to 76 years (mean a e 33 years) had a variety of physiological or pathological conditions established by other criteria and included 120 females and 83 males Methods of obtaining the echocardiograms were after the standard techniques of Feigenbaum All echocardiograms were performed in the left lateral position with the transducer positioned over the third left intercostal space approximately 3 cm from the sternal edge

Fine systolic fluttering of the aortic valve was demonstrated in 35 of the 203 recordings, resulting in a prevalence rate for this finding of 17 2 per cent The distribution of this finding according to normal or disease states is arrayed in Table I If searched for diligently fluttering may be seen in the majority of normal subjects (four of seven or 57 1 per cent) and otherwise healthy young women in the second or third trimester of pregnancy (11 of 14 subjects or 78 6 per cent) Various disease states leading to hyperdynamic circulation also were associated with this echo observation. These included various anemic (< 9 gm per cent blood hemoglobin concentration) states (eight of 12 patients or 66 7 per cent) acquired valvular incompetence of the aortic (three of eight patients or 37.5 per cent) or mitral (six of eight patients or 75 per cent) valves and in three patients with early and mild labile hypertension Conversely in 12 patients with rheumatic valvular aortic stenosis and in four patients with calcific aortic stenosis in which aortic valvular excursions were impaired and the circulation was reduced fine systolic fluttering of the aortic leaflets was not seen

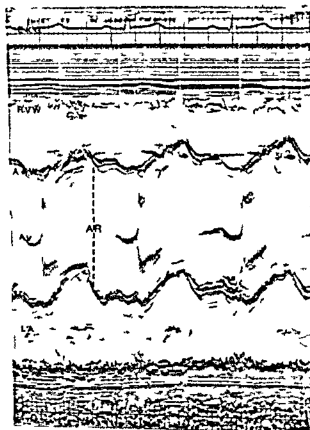


Fig 1 Aortic valve echocardiogram from a patient with non rheumatic aortic regurgitation showing a dilated aortic root and fine systolic fluttering of the aortic leaflets Abbreviations include *ECG* = electrocardiogram *RVW* = right ventricular wall *AAW* = anterior aortic wall *AV* = aortic valve leaflets *AR* = aortic root *LA* = left atrium

The value of echocardiography as a noninvasive bedside tool in the diagnosis and determination of various cardiac conditions is strengthened with each report of new findings of abnormal motion of any of several cardiac structures Demon

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exact site and extent of the conduction abnormality is not known Therefore, the non committal term *non specific intraventricular block* is preferred

Lown Ganong Levine syndrome

By this is meant a form of ventricular pre excitation, which is characterized by a short PR interval and normal QRS complex Generally speaking, eponyms are discouraged, apart from a few historical names The term 'short PR syndrome' is preferred

Monofascicular block

See *fascicular block anterior and posterior*

Myofibrillar block

See *intramural conduction disturbance (LUT)*

Non paroxysmal tachycardia

What is meant in most cases is accelerated impulse formation which may or may not occur in paroxysms (bouts or salvos) (See also *idiofocal tachycardia, NPT*)

Parietal block

See *intramural conduction disturbance (LUT)*

Paroxysmal atrial tachycardia (PAT)

PAT is often diagnosed in cases of supraventricular tachycardia in which the available record does not show paroxysms of tachycardia Furthermore there is disagreement concerning the mechanism and origin (atrial or AV junctional) of these tachycardias Most of these arrhythmias are best indicated by the wider concept of (paroxysmal) supraventricular tachycardia

Peri infarction block

See *intramural conduction disturbance (LUT)*

Pseudo fusion beat

Superimposition of an artificial pacemaker artifact on a spontaneous P or QRS complex This indication serves no special purpose and creates confusion

Return extrasystole

The term 'echo" is preferred

Reversed coupling

Resetting of the SA node by an ectopic atrial or retrogradely conducted AV junctional or ventricular impulse This causes a fixed time relationship between the ectopic impulse and the following sinus discharge Considering the definition of coupling (*see coupling interval*), however, there seems to be no need for the term 'reversed coupling'

Slow tachycardia

This is a contradiction in terms (See also *idiofocal tachycardia NPT*)

Tachyarrhythmia

For some this means a tachycardia with irregular impulse formation or conduction while for others it refers to any tachycardia, regular or irregular (See also *arrhythmia*)

Trifascicular block

Use of the term trifascicular block for various combinations of block in the anterior and posterior fascicles of the left bundle and in the right bundle branch is discouraged Instead, the site, type and severity of the conduction defect should be indicated (See also *bifascicular block LUT*)

Wandering pacemaker

What is meant is an irregular, multiform (multifocal), supraventricular rhythm with changing P wave morphology and varying PR intervals The term wandering pacemaker' is discouraged since it implies a mechanism which is not readily known (See *multifocal rhythm*)

Wedensky effect

The phenomenon in which a subthreshold impulse (stimulus) can result in an effective activation when it is preceded at a given time interval by a maximal or above threshold impulse (stimulus), which itself results in an effective response

Wedensky facilitation

The phenomenon in which during a period of block, a ventricular response causes interruption of the block for variable periods of time

We wish to express our gratitude to the American College of Cardiology for close cooperation The authors also acknowledge the help of Miss Gertrude van Eck Mrs Manja Helmers and Miss Karin Visser in the preparation of the manuscript

Apporopriate therapy of hypertension in the elderly

The wisdom of treating hypertension in the elderly has been queried It has been suggested that anyone over 6o should not be treated

The first consideration is to define "the elderly bearing in mind the implications of that term Certainly over 65 cannot be used as a yardstick. Some few people it is true may be old at 65—but not the majority of a modern Western population In fact, with increasing health care many of one s patients these days remain relatively young and active into their 80 s *Certainly it is my rule to assess a person s age by his mental and physical state and never by his years*

The second consideration is to postulate the benefit of treating hypertension in patients of 65 years or over One has only to consider the folly of a physician not remedying a hypertension of say 200/120 in a man like Sir Winston Churchill when he became Prime Minister of Great Britain in 1940 at the age of 65—or the rashness of a doctor not taking action in the face of a blood pressure of 250/140 in a musician of the caliber of say Rubinstein at the age of 88 to have the answer The benefits of controlling hypertension at any age and indeed in the older age groups have been clearly demonstrated to be a reduction in the incidence of cerebrovascular accidents, cardiac failure renal deterioration and neuroretinopathy Whether a reduction in the incidence of myocardial infarction is achieved as well is open to doubt but it should certainly follow from first principles As the effect of a stroke may if it is not fatal mean long term incapacity for the patient, then the economics alone are worthy of consideration (It is invariably my practice to lower a very high blood pressure in the face of a stroke usually with apparent benefit)

While it is well known that hypertension is better tolerated in women than in men never the less the dangers over the age of 65 appear to be the same

It is also common knowledge that hypertension is self feeding by reason of renal damage and therefore to check the rise in blood pressure may be of positive benefit to a patient even if the underlying causation remain untreated It follows from this last that extensive investigation is not necessarily indicated in the elderly but that benefit may nevertheless accrue from control of the blood pressure

From the above it may be sensed that *in the older groups of patients the management and investigation of hypertension should be flexible and tailored to the individual patient* Included in the assessment of the patient must be his or her personality This is important because by undue investigation and therapy in a particularly anxious person the physician may do more harm than good and many older patients are often anxious either due to slower comprehension or a sense of isolation which may be threatened or real. *Treatment in any case in older patients must be kept as simple as possible*

Treatment is not helped by the fact that many cases of hypertension are discovered casually when the patient is seen for some other unrelated complaint. Such patients can easily come to resent what they may regard as undue interference with their lives especially if the treatment proffered makes them feel ill whereas they probably felt very well before?

The physician will certainly find that whereas some patients will cooperate enthusiastically in proposed regimes others will not In many cases the physician may well have to accept a compromise far from the ideal and hold a watching brief rather than put the patient off altogether to the latter s peril

Having said this when a case of hypertension is discovered in a patient in his sixties or over it is my practice to give a brief physical examination This will include the abdomen (including the femoral arteries) for signs of tumor e g enlarged kidney hypernephroma etc the heart for signs of enlargement aortic disease etc the lungs for signs of cardiac failure the lower limbs for edema and the fundi for arterial assessment An ECG is not performed The urine is checked for albumen sugar and blood—and microscopy and culture are undertaken when indicated The blood is checked for hemoglobin urea lipids and cholesterol—and sugar if there is glycosuria (The lipids and cholesterol are estimated not only for the physician s interest but because I see no reason why the progressive effects of hyperlipidemia and hypercholesterolemia should necessarily go unchecked at whatever age they are discovered. They may indeed be reversible)

Next what level of blood pressure is taken as indicating the need for therapy? I think that any blood pressure of 160/100 worthy of observation in the late 50 s or 60 s and in such cases I have them reviewed by my practice nurse at 6 monthly or annual intervals In the 70 s I am similarly prepared to review blood pressures of 170/110—and in the 80 s blood pressures of 180-190/115 With blood pressures above these levels I institute *gentle* treatment and control certainly paying as much attention to an undue elevation of the systolic pressure as one in the diastolic In the 90-year olds I feel we are dealing very much with special cases and each will be managed on its individual merits' (N B The diastolic pressures given here refer to the fourth phase i e muffling of sounds and not the fifth phase or cessation of sounds.)

The first therapeutic measures will be to correct if possible any etiological factors such as urinary tract infection obesity etc At the same time the blood pressure will be observed at short intervals of a week or two when it is found in some cases that the pressure settles and no therapy is required

If drug therapy is necessary then *it is my practice to proceed cautiously* This holds for people in any age group because patients vary so much in their response to the potent drugs which we nowadays exhibit For instance some patients have a magnificent diuresis with 5 mgm of furosemide—and will be put into a state of collapse by the usual dose of 40 mgm' Similarly a small dose of methyldopa can produce a devastating fall of blood pressure in some people while having little effect in others In older patients such untoward effects may be even more pronounced because of arterial hardening and the slowing of the vasoconstrictor reflexes Certainly the danger of postural hypotension must be constantly borne in mind.

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Fig 2 Fine systolic fluttering in a patient with non rheumatic mitral regurgitation The characteristics and morphology of fluttering are similar to that in *Fig 1* Abbreviations are the same as in *Fig 1*

strations of abnormal aortic leaflet or aortic vascular motion have now been documented in several settings including valvular aortic stenosis bicuspid aortic valves[7] asymmetrical septal hypertrophy[8] flail leaflets in aortic valve endocarditis[9] and dissection of the ascending aorta Less attention has been directed toward the more subtle findings found in apparently normal valves Several workers including Feizi and colleagues Gramiak and Shah and Winsberg[11] have contended that fine systolic oscillations of the aortic valve cusps may be seen in normal leaflets if searched for with sufficient effort The frequency of this finding in normal subjects or its presence in other pathological or physiological conditions was not mentioned The present report suggests its broad occurrence not only in normal controls but in a variety of other settings including pregnancy anemia aortic and mitral valvular regurgitation and labile hypertension While it is as yet premature to suggest an underlying causal mechanism the latter conditions are in many instances characterized by hyperdynamic circulations The fine systolic flutterings may represent an effect of local turbulence on pliable aortic valve leaflets as induced by an altered hemodynamic state Conversely the absence of systolic oscillations in valvular aortic stenosis in spite of equal local turbulence in blood flow may be explained by the thickening of the valve leaflets with resulting restrictions in leaflet movement The finding of high frequency flutters of the aortic valve leaflets in

Table 1 Echocardiograms demonstrating fine systolic flutter*

Condition	*Number demon strated flutter*	*Number studied*
Normal subjects with functional or benign systolic murmurs	4	7
Pregnancy	11	14
Anemia	8	12
Aortic regurgitation	3	8
Non rheumatic mitral regurgitation	6	8
Labile hypertension	3	3
Valvular aortic stenosis	0	16
Totals	35	68

A total of 250 echocardiograms were reviewed of which 203 were used in the study Of these 35 demonstrated fine systolic flutter

the presence of an outflow type murmur (and in the absence of aortic regurgitation) would suggest a pliable normal valve and may therefore provide a useful aid in distinguishing a functional murmur from one resulting from organic valve stenosis

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Table I

	Low altitude saline	Low altitude verapamil	High altitude saline	High altitude verapamil
RV/T ratio	0 ?3 ± 0 01	0 22 ± 0 01	0 37 ± 0 01 †	0 30 ± 0 01 †
No rats	4	5	6	6

 s gnifica tly differ nt from high altit d saline group (P < 0 01)
†S gnifi antly diff re t fr m either low altitud group (P < 0 01)

of hypoxic pulmonary hypertension was assessed by measur ing the degree of right ventricular hypertrophy using the ratio of the weight of the free wall of the right ventricle to the total ventricular weight

Treatment with verapamil did not affect left ventricular weight nor did it affect the hematocrit (low altitude 45 per cent high altitude 63 per cent) suggesting that the hypoxic stimulus was the same in verapamil and saline treated groups. The values shown indicate that saline treated high altitude rats developed more right ventricular hypertrophy than verapamil treated animals The smaller degree of right ventricular hypertrophy in high altitude rats treated with verapamil was presumably due to a lower level of hypoxic pulmonary hyp rtension This finding is consistent with the observation that verapamil inhibits the pulmonary pressor response to acute alveolar hypoxia The possibility of similar hemodynamic effects in man should be considered by physi cians using verapamil for its cardiotonic or anti hypertensive effects.

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Of why the two heart pumps are anatomically united to form one heart

The heart is composed of two separate pumps which are separated circulatorily by the pulmonary vascular system and the systemic vascular system As indicated previously the two separate pumps must be properly synchronized and integrated in their pumping of blood or the distribution of blood volume throughout the entire circulation would be seriously disturbed and either acute pulmonary congestion with acute pulmonary edema would result or the pulmonary vessels would become emptied of blood To appreciate this fully a previous publication should be studied closely

It is interesting to speculate why there is a two pump cardiac system and why the two pumps are closely anatomi cally intertwined to form one anatomic heart This arrange ment is an important efficient and desirable one For exam ple were the right and left sides of the heart—the two pumps—completely separated pulmonary conge tion would suddenly occur if supraventricular or ventricular tachycardia developed in the independent and anatomically separate ri ht heart while the left atrium and left ventricle continued to contract 0 or so times per minute More blood would be ejected into the pulmonary vessels by the right pump than would be removed from these vessels by the left pump Were the left atrium or ventricle to develop supraventricular or ventricular tachycardia more blood would be removed from the pulmonary vessels than would be pumped into them by the separate right heart pump and the pulmonary vessels would become dry or essentially empty These states would result in serious and acute circulatory disturbances and even death of the individual On the other hand with the right and left pumps joined anatomically as they are both pumps respond essentially simultaneously to tachycardias or extra systole Neither side of the heart can fibrillate or contract separately This arrangement usually (I can think of excep tions) assures a well balanced circulation which is essential for a good circulatory state as indicated elsewhere even in the presence of arrhythmias which are initiated in either the right or left pump

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It is my practice to prescribe initially small doses of a mild diuretic—usually a thiazide (but bearing in mind these drugs diabetogenic qualities) The patient s own observations as to effect will be carefully listened to and considered as well as recording the response of the blood pressure and apex rate If necessary the dose can be cautiously increased If the blood pressure still remains at a higher level than is desired it is my practice to add on small doses of either a beta blocker (propranolol) or methyldopa or clonidine or rarely bethanidine or guanethidine

Again it must be emphasized that *with older patients caution must be the keynote of therapy* and small doses must be used initially with frequent assessments made of the response obtained—say every three to seven days These assessments will be made by the practice nurse the doctor advising with regard to dosage etc Self monitoring by the patient is probably by and large unsatisfactory but may be possible with some

Once satisfactory control has been achieved it is essential to monitor the patient from time to time—say at three or six monthly intervals As the years go by the older patients blood pressure will be found to drop if therapy has been maintained—presumably due to progressive myocardial degeneration In such cases it will be essential to reduce the dosage of the treatment (The onset of Addison s Disease will also be discovered in the elderly—particularly if it is borne in mind and looked for!) Those patients taking methyldopa should have a periodical Coomb s test and hemoglobin estimation The urine especially of those patients taking thiazides should be periodically checked for sugar and the electrolytes of any patient taking a diuretic should be borne in mind as with the blood urea and uric acid Infection and warm weather may dramatically lower the blood pressure especially in the elderly and this must not be lost sight of Depression is a side effect of both beta blockers methyldopa bethanidine and guanethidine *and should be looked for* (I no longer use the rauwolfia alkaloids for this reason) Clonidine may cause *mental disturbance* Impotence with all these drugs may be a problem The dangers of the beta blockers in asthma diabetes and cardiac failure must not be overlooked nor the fact that there is some evidence that they are contraindicated in generalized psoriasis and systemic lupus erythematosus The onset of a paroxysmal heart block may pose problems only soluble by the use of a pacemaker

It should be re emphasized that the *drug regime should be kept as simple as possible* so that it will not only be understood but taken properly by the patient There is probably a place here for some of the combined preparations which many of us are normally loath to prescribe

In conclusion it may be said that hypertension is a disease *par excellence* of the elderly Over the age of 65 the systolic blood pressure can climb dramatically The treatment of hypertension in such elderly patients is rewarding both in terms of health and economics *provided that it is done with due care and caution* This treatment may be undertaken relatively simply and at comparatively small cost

My thanks are due to Dr H G Mather M D F R C P of Bristol for his help and advice with the preparation of this annotation

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Pulmonary vascular effects of verapamil

Verapamil a synthetic compound related to papaverine is currently under study as an anti arrhythmic and antihypertensive agent It depresses transmembrane calcium influx in cardiac[2] and vascular smooth[3] muscle thereby resulting in membrane stabilization We have shown that verapamil inhibits the pulmonary pressor response to acute alveolar hypoxia in isolated rat lungs and anesthetized dogs We wondered whether verapamil would depress the development of pulmonary hypertension during *chronic alveolar hypoxia Therefore* we exposed 250 gram male Sprague Dawley rats to local altitude (1 600 M) or to a simulated high altitude (5 500 M) in a hypobaric chamber for 20 days Half the rats at each altitude received 4 mg verapamil in 0 5 c c saline intraperitoneally twice a day and the other half received only saline The degree

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alternating with re entrant extrasystoles (manifested and concealed)

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1 Kinoshita S Concealed ventricular extrasystoles due to interference and due to exit block Circulation 52 230 1975
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Reply

To the Editor

I appreciate and welcome Dr Kinoshita s interest and his suggestions regarding the phenomena observed in my case of intermittent parasystole with concealed bigeminy

Dr Kinoshita has obviously shown innovative expertise in the complex rarer manifestations of intermittent parasystole and concealed bigeminy as exemplified by both his and my bibliography

I, myself was perplexed to explain the successive cycle length shortening in each parasystolic series and proposed several mechanisms in my discussion Dr Kinoshita has demonstrated in previous articles (his references 1 to 3) that there is often a relative refractory period late in an intermittent parasystolic cycle length and that either complex alterations in resetting or re-entrant extrasystoles can result because of entrance or exit block conduction delay His proposed mechanism of re entry however would explain only isolated abbreviation of terminal cycle lengths As shown in my table cycle lengths tended to gradually shorten during a parasystolic series although some even lengthened including the last cycle

If each parasystolic cycle length were divided into two parts, with one interval being from parasystolic to conducted beat and the other interval from conducted to parasystolic beat and a curve were constructed plotting these intervals against each other one would see a reciprocal relationship with a slope of identity Only 4 points out of 60 deviated from this curve These points all demonstrated short coupling intervals (0 46 to 0 51 sec) to preceding conducted beats relatively long intervals between parasystolic and the following conducted beats (1 16 to 1 20 sec) approaching the end of the parasystolic refractory period (1 22 sec) and were also terminal cycle lengths in a parasystolic series These beats could well be re-entrant as suggested by Dr Kinoshita

Levy and Kenn have recently described two cases which demonstrated rhythm sequences and interval changes identical to those of my case report and have formulated an entirely different mechanism which excludes intermittent parasystole They proposed re entry extrasystolic loops with various sites of block to explain both their and my observations of even number sequences of conducted beats between ectopic series and single conducted beats during ectopic series. The progressive shortening of both coupling intervals and interectopic intervals during a bigeminal sequence was thought secondary to a positive feedback system in a re-entry loop rather than to an intermittent parasystolic mechanism This re-entry formulation could possibly explain the phenomena in my case and is essentially a more complicated modification of Dr Kinoshita s suggestions

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More on effectiveness of the CCU

To the Editor

In a recent annotation Dr Lindholm and colleagues write that no well-controlled study has as yet been reported about the effectiveness of coronary care units (CCU) in reducing the mortality of acute myocardial infarction although CCUs offer a certain marginal gain as some patients are resuscitated who would otherwise have died Regarding this latter affirmation we feel that what is marginal in mortality rate perhaps is not so for the patient and for his family Moreover it must be stressed that results of all present medical activities are disappointing as far as the mortality rate is concerned[1] This does not hinder us from treating patients medical activity in most cases has always reached individual results.

Dr Lindholm and associates also write that the results of CCUs could be achieved in many other diseases provided that the patients were (or could be) as carefully supervised as in CCUs. It is desirable that this be done but we doubt that results of CCUs could be obtained Results of CCUs in acute myocardial infarction depend indeed on saving hearts which anatomically are too good to die It seems there are not many similar situations in the pathology of other organs

Instead we completely agree with Dr Lindholm and coworkers when they affirm that CCUs must not be too numerous for this WHO has given appropriate instructions We add also that CCUs must not be expensive CCUs essentially prevent deaths from arrhythmias for this ECG monitoring is of foremost importance Only ECG monitors and defibrillators are fundamental, and well trained attendants and dedicated doctors and nurses remain imperative A CCU with only these essential elements perhaps is no more a CCU But too many CCU are only a useless exhibition of electromedical instrumentation

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Parasystole and re entry

To the Editor

I read with much interest the report by Dr Lightfoot on intermittent ventricular parasystole with concealed extrasys tolic bigeminy (THIS JOURNAL 93 229 1977) I agree with Dr Lightfoot on all of the explanations suggested in his report except for the following finding His case showed that the last ectopic cycle length in each parasystolic series was usually the shortest in the series For this finding I would like to offer an explanation different from that suggested by Dr Lightfoot The mechanism suggested by me is illustrated in Fig 1 in which the early portion of the bottom strip of panel *B* shown in Lightfoot s Fig 2 is diagrammatically represented

As pointed out by him the last interectopic interval E_4 E in the first parasystolic series of Fig 1 here is the shortest in the series which measures a period of 168 (All of the time *intervals in this letter* are expressed in hundredths of a second) This last interectopic interval E E is definitely shorter than either of the preceding interectopic intervals E_1 E and E E Dr Lightfoot considered that the ectopic beats including the last ectopic beat in each series were all parasystolic beats On this assumption he explained that the refractory period of the parasystolic focus s protection from conducted sinus beats was a period of 122 or 124 and that the parasystolic rate tended to slightly accelerate during each series owing to a warming up of the ectopic pacemaker

An alternative explanation for the above finding is illus trated by the diagram in Fig 1 The interectopic interval E E_4 (i e a period of 179) is not shorter than its preceding interectopic interval E_2 E_3 (i e a period of 177) namely acceleration of the parasystolic rate is not seen here The conducted sinus impulses preceding these ectopic beats i e the impulses S_2 S and S fall in the refractory period of the ventricular ectopic (V E) junction and therefore the ectopic focus is protected from these impulses However the V E refractory period here is somewhat shorter than that suggested by Dr Lightfoot so that the conducted sinus impulse S preceding the last ectopic beat in the series falls shortly after the V E refractory period Thus after marked delay the sinus impulse S reaches and discharges the ectopic focus with resetting of the parasystolic rhythm *After that the impulse S becomes a re entrant extrasystole E_5 Namely* the ectopic beat E_5 is not a parasystolic beat Therefore the last interectopic interval in an ectopic series is the shortest in *the series not because the parasystolic rate tends to acceler* ate but because the last ectopic beat in the series is a re entrant extrasystole Shaded areas in the diagram represent *the refractory period*

On the other hand the conducted sinus impulse S subse quent to the re entrant extrasystole E falls long after the V E refractory period and therefore it reaches the ectopic focus after not enough delay to become a re entrant extrasystole In other words it becomes a concealed extrasystole due to interference so termed by Kinoshita The conducted sinus impulses S S and S fail to disturb the parasystolic rhythm because they interfere with the parasystolic impulses (E) (E_6) and (E) respectively within the V E junction and cannot reach the ectopic focus as suggested in my previous report The sinus impulse S_{16} and the parasystolic impulse E interfere within the ventricles indicating a ventricular fusion beat

Such a marked conduction delay within the V E junction as suggested in this letter was also indicated in my recently reported cases of intermittent ventricular parasystole[2,3] In one of these cases when a sinus impulse fell shortly after the V E refractory period it reached the parasystolic focus after marked delay and thereafter became a re entrant extrasystole showing the same configuration as that of the parasystolic beats Warming up of the ectopic pacemaker i e accelera tion of the ectopic rate usually occurs after the ectopic focus is repeatedly discharged at a markedly rapid rate in compar ison with the basic rate of the ectopic pacemaker In intermit tent parasystole however the parasystolic pacemaker cannot be repeatedly discharged at such a rapid rate because the refractory period of the parasystolic focus s protection is markedly prolonged Thus I think that the case of Dr Lightfoot may probably show intermittent parasystole

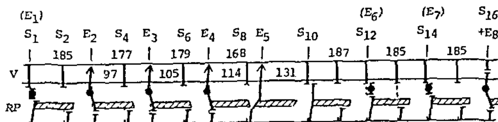


Fig 1 Diagram illustrating intermittent ventricular parasystole alternating with re entrant extrasystoles (manifested and concealed) Time intervals are expressed *in hundredths of a second Shaded areas represent the* refractory period Intraventricular conduction of the sinus (or ectopic) impulse leading to the ventricular ectopic junction is indicated by dashed lines S = sinus impulse conducted to the ventricles E and *(E)* = ectopic beat and concealed ectopic impulse respectively $S + E$ = *ventricular fusion beat* V = *ventricles* RP = re-entrant path containing the ventricular ectopic junction the parasystolic focus and the ectopic ventricular junction

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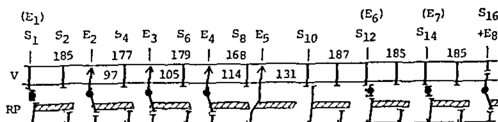


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Book reviews

Non invas ve Clinical Measurement Fdited by David Taylor and Joan Whamond Baltimore 1977 University Park Press 205 pages Price $39 0

This book is edited by Taylor and Whamond of the Department of Applied Physiology and Surgical Sciences of the Royal College of Surgeons of England The book consists of several papers gathered into three sections namely blood flow in large arteries blood flow in the peripheral circulation and orthopedics obstetrics and respiration The presentations are directed primarily to the clinical aspects of non invasive clinical measurements particularly the use of various aspects of ultrasound recordings. The applications of Doppler shift for measuring the adequacy of blood flow is emphasized Impedance recording is discussed as are other graphic and semigraphic technics for measuring blood flow primarily in the limbs Unfortunately these editors fail to include in the discussion the importance of the history and physical exami nation or the conditions of the examining room and table and the patient s bed The book is concerned primarily with blood flow in large blood vessels The small peripheral vessels are not adequately considered The use of plethysmography thermog raphy and thermocouple or thermistor recordings are essen tially ignored This is to be expected because of the nature of the interest and applications intended The discussions presented are good and should supplement very well other sources of study in the medical literature related to peripheral vascular disease

Exercise Testing of Cardiac Patients By M Kaltenbach Baltimore Md 1976 The Williams & Wilkins Company 126 pp

This monograph of the series of *Monographs on Standard ization of Cardio Angiological Methods* reviews in detail the various methods used for exercise testing of cardiac patients The methods reviewed are numerous and clearly discussed The treadmill used so extensively in the U S A at present is not presented in detail Neverth less this 126 page paperback monograph is useful and should be carefully studied by all cardiologists It outlines v ry well the many problems involved in exercise testing Illustrations clearly show the direct relationship of oxygen consumption to the degree of exercise The close positive relationship is to be expected but the fin lings do show the effectiveness of the exercise testing methods in recording the quantity of O consumption according to the extent of exercise It is evident from this book that th interpretation of the ECG obtained with exercise testing is often very difficult if not impossible The fact that the ECG changes reflect cardiac function with physical stress is interesting These changes are simple to record and at times useful clinically Because of the intense interest in exercise testing this book should be studied by all physicians who treat heart disease This is a good book but unfortunately for physicians in the U S A it contains only a brief discussion on the use of the treadmill exercise testing method

Cardiac Pacing Edited by Yoshio Watanabe Amsterdam Oxford 197‹ Excerpta Medica 601 pages

This book contains the papers presented at the Fifth International Symposium on Cardiac Pacing in Tokyo during March 1976 The papers are numerous and brief They are concerned with cardiac electrophysiology A V block hemodynamics of pacing as a diagnostic tool treatment of arrhyth mias long term follow up of implanted pacemakers malfunc tion engineering and testing energy sources and electrodes There are good sections of discussions and there is a good round table discussion on the question Is pacing prolonging life? This question is discussed by contributors from everal nations.

The book is a good one Its importance is evidenced by the common use of pacing in medicine It is unfortunate that each presentation is so brief Nevertheless the reader will learn from this book the opinions on pacing from physicians throughout the world It is a good book which is organized in the same manner as all other proceedings of meetings and symposia

The Evan Bedford Library of Cardiology Catalogue of Books Pamphlets and Journals London 1977 Royal College of Surgeons

This is a catalogue of the excellent collection of the Library of Cardiology of Dr Evan Bedford of London Those who knew Bedford admired him for his interest in fine things as well as for his ability as a bedside clinician Bedford had been collecting rare books and other classics in cardiology for many years. This book lists the books and briefly describes the authors their interests and the contents of the various books Many of these publications this reviewer had not known The listing classification and description of the many (over 1 000) books and pamphlets were extremely well done and with excellent taste Bedford wisely gave the collection to the Royal College of Physicians of London where they will remain where Bedford practiced and taught. This is a useful publica tion describing the contents of this fine collection

2 Burch G E People live no longer anymore AM HEART J **83** 285 1972
3 Goldstein S Sudden death and coronary heart disease Pathology of sudden death Mt Kisco N Y 1974 Futura Publishing Company
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MLAP LVEDP and left ventricular dysfunction

To the Editor

We would like to make a comment on a statement mentioned by Kouchoukos and Karp in their excellent review of Management of the postoperative cardiovascular surgical patient (Am Heart J 92 513 531 1976) They stated that mean left atrial pressure (MLAP) in the absence of either stenosis or incompetence of the mitral valve approximates left ventricular end diastolic pressure (LVEDP) (page 517) This statement is true in the case of normal left ventricular (LV) function but it may not be so in patients with left ventricular dysfunction or in postoperative cardiovascular surgical patients since the LVEDP is not equal to MLAP in the presence of left ventricular disease Braunwald and Frahm have shown that the difference between LVEDP and MLAP is between 1 and 18 mm Hg with an average of 9 0 mm Hg in all 21 patients with left ventricular disease in whom the pressures were measured none of these patients having mitral valve disease

It is not uncommon to detect very high LVEDP in the range of 25 mm Hg or more in patients with coronary artery disease (CAD) while angina free yet they are not in congestive heart failure (CHF) indicating that their MLAP is lower than their LVEDP

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2 Braunwald E and Frahm C J Observations on the hemodynamic functions of the left atrium in man Circu lation **24** 633 1961

Reply

To the Editor

Drs Haddad and Prokhov are correct in pointing out that differences between left ventricular end diastolic pressure and mean left atrial pressure may exist in patients with left ventricular disease who are in normal sinus rhythm as described by Braunwald and Frahm[1] However in a study of postoperative hemodynamics in 11 patients who had mitral valve replacement and in one patient who underwent excision of a left atrial myxoma by Rastelli and Kirklin no statisti cally significant difference between 42 simultaneous determi nations of mean left atrial pressure and left ventricular end diastolic pressure was observed In this group of patients evidence for impaired cardiac function was present (i e low cardiac output and elevated left ventricular filling pressure) All but one of these patients were in atrial fibrillation Our assumption is based on these observations and on observations of the response of measured left atrial pressure and cardiac output to infusion of volume vasodilating and inotropic drugs in a large number of postoperative cardiac surgical patients many of whom are described in our paper While we agree that the measurement of mean left atrial pressure may not accurately reflect left ventricular end diastolic pressure in all circumstances it has proved a most useful parameter for assessment of cardiac performance postoperatively and as an index of the response to various interventions to increase preload decrease afterload and increase myocardial contrac tility

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2 Rastelli G C and Kirklin J W Hemodynamic state early after prosthetic replacement of mitral valve Circu lation **34** 448 1966

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George E Burch *Editor*

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Books received

An Atlas of Heart-Lead Coefficients By Stanley Rush Hanover New Hampshire 1977 University Press of New England 211 pages Price $45 00

Vascular Surgery 1st edition Edited by Robert B Rutherford M D Philadelphia 1977 W B Saunders Company 1 401 pages *Price $65 00*

Doppler Ultrasonic Assessment of Cerebrovascular Disease By Robert W Barnes and Michael R Wilson Iowa City 1975 *University of Iowa 187 pages*

Doppler Ultrasonic Assessment of Peripheral Arterial Disease By Robert W Barnes and Michael R Wilson Iowa City 1976 University of Iowa 275 pages

Announcements

Continuing Education Symposium on Nutrition

The Division of Continuing Education in the Health *Sciences Schools of Dentistry Medicine Nursing* and Pharmacy University of California San Francisco and The Institute for the Study of Human Knowledge will present a symposium entitled Nutrition *Myths and Realities to be* held in San Francisco California on June 3 and 4 1978 The symposium is approved for AMA Category I credit For further information contact University of California San Francisco Continuing Education in Health Sciences 1308 Third Ave San Francisco Calif 94143 Telephone (415) 666 2894

IX International Congress for Heart Research

The IX Congress of the International Society for Heart Research will be held in New Delhi India from September 28 to October 2 1978 In addition to several Symposia and free communications there will be a competition for the Richard Bing Award for Young Investigators For inquiries please write to Prof P K Das Department of Physiology Faculty of Medicine University of Manitoba Winnipeg Canada R3E OW3

Diagnostic Heart Imaging symposium

A symposium on Diagnostic Imaging of the Heart will be held at the Orlando Hyatt House Disneyworld Fla on August 2 through 6 *1978 The symposium sponsored by the* University of South Florida College of Medicine carries 20 hours of AMA Category I credit Fee for physicians is $175 U S *funds* fee for residents and technicians is $95 U S funds For further information contact Lawrence R Muroff M D Educational Symposia P O Box 17241 Tampa Fla 33682

International symposium on exercise and cardiovascular function

The Czechoslovak Society for Rehabilitation and the Czechoslovak Society of Cardiology are organizing under the protection of the Rehabilitation Council of the International *Cardiological Society President Prof Dr H Denolin* an International Symposium on exercise and cardiovascular function to be held on October 11 through 13 1978 in Bratislava CSSR (Czechoslovakia) Topics will include

(1) Influence of Exercise on Circulation (Physiological and Pathophysiological Aspects)

(2) Exercise in the Rehabilitation Programs in Cardiovascular Diseases and

(3) Free Communications

For further information contact Miroslav Palát M D Dept of Physical Medicine and Rehabilitation Derer s Hospital Limbova ul 809 46 Bratislava Kramáre ČSSR or Slovak Medical Society Congress Office Mickiewiczova 883 *22 Bratislava CSSR*

Information for authors

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Your confidence in Intermedics is as important to us as your patient s confidence is to you That s why we want you to know about the InterLith[T] chosen around the world as one of the most reliable pacemakers available

Intermedics supports the outstanding reliability of the InterLith and will allow a replacement on model 223 generators which fail for any reason during the lifetime of the original user

Extensive use has confirmed its outstanding performance and reliability resulting in an annual failure rate of only 003 at the 90 % confidence level with no reported failures of its lithium power source

In addition to its proven reliability the InterLith has significant features which make it an especially fine choice as a replacement pacemaker such as a universal connector that readily accepts most leads without an adapter So when your patient needs a pacemaker for whatever reason consider the InterLith model 223 a pacemaker with which you can feel confident

Confidence begins with extraordinary design features

A tungsten inert gas (TIG) welding technique is used to hermetically seal the InterLith in a 316L stainless steel enclosure that prevents moisture leakage A specially designed polycrystalline ceramic feedthrough seal utilizing a 99 99 / pure platinum conductor makes the electrical connection to the pulse generator The high collar design of the feedthrough minimizes fluid leakage in the harsh environment of the human body

The patient lifetime replacement agreement is limited to the standard model 223 pulse generator and does not include the 223-02 (High-Output) pulse generator Consult the physician s handbook for these special" pacemakers for their specific patient replacement agreements

The InterLith is one of the smallest lightest pacemakers on the market Its corners are gently beveled much as the contours of the patient s own body minimizing the risk of pressure necrosis The unipolar model weighs only 75 grams and measures 6 0 cm by 4 6 cm by 1 5 cm enabling a smaller incision and a more cosmetic pocket for greatest patient comfort The InterLith pacemaker provides the physician with an ideal choice for many pacing situations

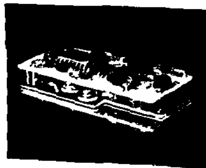
Confidence increases with superior performance

The InterLith s annual failure rate of less than 003 (at 90% confidence level) is largely attributable to the outstanding longevity of its lithium power cell a battery without a single failure reported in 150 000 battery units manufactured Combined with the proven reliability of c mos circuitry the InterLith provides superior performance at the lowest possible power consumption This design represents sophisticated state of the art technology in pacemaker electronics and gives the InterLith an outstanding theoretical longevity

Quality control ensures confidence

Every component utilized in the InterLith is selected and tested to meet the same standards as in the most exacting aerospace and military applications Every step of the manufacturing process at Intermedics is subject to rigid quality assurance procedures in our complete environmental testing laboratory because at Intermedics we believe only the highest quality products can merit your confidence Some of the high reliability screening steps that our pacemakers receive in manufacturing are

1 Twenty four hour dynamic temperature cycling from −30° to +80 C
2 Vibration testing at 1 displacement and 10 g s from 20 HZ to 2 KHZ
3 Strip chart rate recording from room temperature to 60 C
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The InterLith is designed and built for the confidence of you and your patients

So the next time one of your patients requires pacing therapy why not select the InterLith Where reliability counts there s no better choice



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